Resuscitating the Bioweapons Ban: U.S. Industry Experts' Plans for Treaty Monitoring

A Collaborative Research Report
of Experts from the U.S. Pharmaceutical and Biotechnology Industries

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Preface

This report is a collaborative effort between the Center for Strategic and International Studies (CSIS) and a group of U.S. biopharmaceutical experts. Previous groups of industry experts developed an inspection hypothesis that countered the prevailing view that it is impossible to monitor the Biological and Toxin Weapons Convention (BWC) effectively without compromising trade or defense secrets. Building on the recommendation of a previous group of industry experts, CSIS invited over a dozen senior industry scientists and managers to develop detailed plans for trial inspections to test the proposed strategy and techniques for protocol for monitoring the BWC at industry facilities. CSIS is truly fortunate these experts with such incredible credentials stepped forward to execute this task. Recognizing the technical and policy contributions that made the U.S. chemical industry such a valuable partner in crafting monitoring procedures for the Chemical Weapons Convention, CSIS believes that this report demonstrates that the U.S. pharmaceutical and biotechnology industry can play an equally admired and definitely needed role in strengthening the bioweapons nonproliferation regime.

True to their backgrounds as industry insiders, the work of this group of experts balances the needs of treaty inspectors with industry's interests in protecting proprietary information. This project would not have been possible without the active participation of the all of the industry experts involved. The bedrock of this report is the scientific expertise and industry acumen of this group of busy professionals. Despite hectic schedules, they convened in mid-March and mid-June to elaborate their inspection hypothesis, where needed, and formulate trial inspection plans. Several experts took assumed additional responsibilities for providing the first drafts of the protocols and evaluation forms contained in this report. They also offered constructive comments throughout the drafting of the report.

The experts who participated in the 2004 industry working group are:

- Will Carpenter, a Ph.D. plant physiologist with a distinguished career of over 30 years at Monsanto, shared his experience as a principal representative of the U.S. chemical industry during the trial inspections and negotiations that produced the Chemical Weapons Convention;
- Kenneth Coleman, a Ph.D. microbiologist who holds several patents and currently heads the Clinical Microbiology Group at AstraZeneca's research and development facility in Boston;
- Ian A. Critchley, the senior director for microbiology at Replidyne, Inc., who holds a Ph.D. in microbiology and spent a decade with SmithKline Beecham prior to joining Replidyne;
- Robert Goldberg, who has a Ph.D. in medical microbiology and recently retired after over 30 years involved in industry and in research institutes, a career capped as the executive director for strategic and scientific planning at a pharmaceutical company in the top 25 of the Fortune 100;
- Dennis Gross, a Ph.D. cell biologist and industry veteran of more than 25 years who is double-hatted as an adjunct professor of biochemistry and molecular pharmacology at Thomas Jefferson University's College of Medicine and College of Graduate Studies;
- Jennie Hunter-Cevera, a Ph.D. microbiologist and president of the University of Maryland Biotechnology Institute, where she draws on over 20 years of industry experience to incubate new products and technologies;
- Douglas Jaeger, who was the 2003-2004 president of the Society for Industrial Microbiology and topped off a 35-year industry career as the manager of custom fermentation and bioprocessing for a U.S. pharmaceutical firm with over $15 billion in annual revenues;

- Robert Maigetter, vice president of operations for Immunomedics, Inc., who has a Ph.D. in microbiology and over 25 years in research and management at Immune Response Corp. and Merck before joining Immunomedics;
- Frank J. Malinoski, executive vice president and chief medical office of a major U.S. biopharmaceutical company, and a former inspector of bioweapons activities in the Soviet Union and Iraq who is both a physician and a Ph.D. microbiologist;
- Claude Nash, vice president of the University of Maryland Biotechnology Institute, a Ph.D. in microbial genetics and biochemistry who started his own biotechnology company after 30 years with major pharmaceutical firms;
- Kay Noel, a Ph.D. biophysicist who draws on over 20 years of industry experience in commercial development, project management, and marketing as a consultant for biotechnology and healthcare companies around the globe;
- George Pierce, professor of applied and environmental microbiology at Georgia State University, a Ph.D. microbiologist who after over 20 years in industry left Cytec Industries as a manager of technology development and engineering;
- James Poupard, president of the Pharma Institute of Philadelphia, who holds a Ph.D. in history and philosophy of science and whose last position after over 40 years of experience was as director of strategic microbiology in the Research and Development division of GlaxoSmithKline; and,
- George Robertson, vice president for the science and technology division of the PDA, a 30 year veteran of the biopharmaceutical and biodefense industries who served as a bioweapons inspector in Iraq and has a Ph.D. in molecular biology.

Appendix 1 contains short biographies for each of these individuals. All made worthy contributions to this project and are deserving of much more than a simple "thank you."

From the American Chemistry Council, Mr. Mike Walls and Ms. Marybeth Kelliher from the American Chemistry Council should also be recognized. They attended the brainstorming session on 9 March 2004 to share lessons learned from the chemical industry's trial inspections as well as from the industry's experience with the implementation of the Chemical Weapons Convention. Ms. Angela Woodward of the Verification Research, Training and Information Centre was also attended the mid-June brainstorming two meetings, adding a European view to the proceedings.

The author would also like to thank the Nuclear Threat Initiative, whose generous grant enabled this project to draw on the technical expertise of the U.S. biopharmaceutical industry for the purposes of strengthening the Bioweapons nonproliferation regime. Dr. Mark Smolinksi, senior program officer of NTI's Biological Programs, deserves special thanks for his stewardship of this endeavor. A debt is also owed to Dr. Margaret Hamburg, NTI's vice-president for biological programs at the onset of this initiative.

Last, and as the saying goes, not least, credit is due to Mr. Darby Parliament and Mr. Nate Reynolds of CSIS International Security Program. The former was the glue that kept the brainstorming meetings from falling apart. Moreover, Mr. Parliament did considerable heavy lifting on the first draft of this report. For his part, Mr. Reynolds provided the research and editing assistance so essential to bringing a report of this size and complexity across the finish line. My appreciation of this dynamic duo is most sincere.

A.E.S.
Washington, DC
November 5, 2004

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List of Abbreviations

BWC	Biological and Toxin Weapons Convention
CBM	confidence-building measure
CFR	Code of Federal Regulations
CWC	Chemical Weapons Convention
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
GMP	Good Manufacturing Practices
HEPA	High efficiency particulate arresting (filter)
HVAC	Heating, ventilation, and air conditioning system
IAEA	International Atomic Energy Association
NIH	National Institutes of Health
NPT	Nuclear Non-Proliferation Treaty
OPCW	Organization for the Prohibition of Chemical Weapons
PhRMA	Pharmaceutical Research and Manufacturers of America
PCR	Polymerase Chain Reaction
R&D	Research and Development
USAMRIID	U.S. Army's Medical Research Institute of Infectious Diseases
VEREX	Ad Hoc Group of Verification Experts

Executive Summary

The vigorous pace of discovery and innovation in the life sciences is dramatically increasing the world's ability to recognize and combat diseases, remediate the environment, and increase harvests, among other things. At the same time, the potential for biotechnology to be misappropriated for malevolent purposes is most worrisome. While the vast majority of pharmaceutical and biotechnology activity worldwide has peaceful intent, the USSR and Iraq confirm the ability to proliferate biological weapons clandestinely under the guise of legitimate commercial activity. These circumstances highlight the vulnerabilities of the Biological and Toxin Weapons Convention (BWC), the international treaty that bans the development, production and stockpiling of germ weapons.

Unlike its nuclear and chemical counterparts, the BWC has no formal means of monitoring treaty compliance. Policymakers, industry officials, and the general public are commonly told that the BWC is "unverifiable" due to the complex, dual-use nature of biological materials, equipment, and technologies and the claim that inspections would automatically reveal sensitive defense or business information. These assertions hang in the air unchallenged because international negotiations to strengthen the BWC with the addition of a monitoring protocol collapsed in 2001. No movement is afoot to revive such talks. Moreover, the Executive Branch has not fulfilled the obligations of a 1999 U.S. law requiring a thorough experimental and analytical assessment of the capabilities and limitations of on-site inspections for monitoring BWC compliance.

The Industry Experts' Proposal

Recognizing that judgments about the likely effectiveness and costs of a BWC monitoring regime are being made in the absence of factual data and a basic cost-benefit analysis, a group of U.S. pharmaceutical and biotechnology industry experts is openly skeptical of the premature conclusion that the BWC is unverifiable. These experts, who share over 330 years of varied industry experience and whose short biographies can be found in Appendix 1 of this report, crafted a detailed proposal to monitor the BWC at industry facilities. The Center for Strategic and International Studies hosted meetings in March and June 2004 with these industry veterans, wherein they designed detailed plans to test their monitoring approach during trial inspections at U.S. bio-pharmaceutical facilities engaged in development and manufacturing activities. The industry experts propose such field tests as essential to both the technical and policy foundations needed to bolster the international regime against biological weapons.

The industry experts view the U.S. pharmaceutical and biotechnology industry as a vital partner with vested interests in determining the technical feasibility of monitoring the BWC. Therefore, the industry experts' inspection plans are guided by such key principles as:

- Balancing monitoring activities to determine treaty compliance with the need to protect proprietary data;

- Testing the feasibility of BWC compliance monitoring at industry sites in a manner that starts with basic proof of concept and graduates to increasingly more complex, demanding trials, in complete consultation with host facilities as inspection techniques are refined; and,
- Minimizing the burden on facilities hosting trial inspections while nonetheless sharing the lessons learned from the trials with interested parties in the United States and abroad.

In a kickoff meeting, companies that are considering volunteering to host a trial would be briefed extensively about the proposed trial inspection process and their obligations as trial hosts. A BWC monitoring trial would officially begin with a second tabletop exercise to allow the trial inspectors to review site-specific open source data and customize their inspection tactics and team membership to be able to conduct the on-site inspection most efficiently and effectively. Each trial will conclude with post-inspection evaluation and reporting activities.

The industry experts designed an on-site inspection strategy that is multi-layered and deliberately overlapping in places. From the moment they arrive at the facility, the inspectors will be pinning their assessments and actions on the inconsistencies that they encounter with normal scientific and industrial practice. The industry experts anticipate that the on-site trial inspection activities would consume five days. On-site activities include:

- An initial site tour, including an inspection of the facility's strain collection(s) and taking a final product sample, to acquaint the inspectors quite thoroughly with the site and act as a springboard for subsequent inspection activities;
- A document review involving numerous and intentionally cross-referenced records, virtually the lifeblood of the inspection because it has the potential to reveal and explain so much;
- An interview phase marked by sit-down discussions and additional talks with staff on the production line or in laboratories; and,
- The cross-checking of information to validate particularly important facts, to explore the reasons for inconsistencies, and to help inspectors assess whether the facility's activities make sense from an operational, scientific, and financial perspective.

The industry experts were mindful of companies' needs to safeguard proprietary business information as they designed both their inspection hypothesis and their trial inspection plans. Reflecting one of the many balances in their overall inspection formula, the industry experts stipulated that companies can redact confidential data unrelated to BWC compliance from documents.

Aside from poring through documents, the industry experts agreed that sampling would be the strongest tool to reveal any "smoking guns" during an actual (non-trial) inspection. For the first trial and during any routine inspection of a manufacturing facility, the only

sample automatically taken would be of a final product. They propose some sampling protocols in this report and see trial inspections as the venue to test and refine to the satisfaction of industry and the inspectors additional sampling protocols based on pre-validated sampling and analysis techniques.

The industry experts assert that highly skilled inspectors using their specified monitoring strategies and techniques should be able to discern legitimate facilities from those that mask illicit weapons activities. Trial inspectors should be a "dream team" from the bio-pharmaceutical industry, academics with industry experience, and retired government officials. Other key trial inspection participants are an observer from the host site and an independent ombudsman, both of who will be privy to all aspects of the trial and will provide separate evaluations of the events. To minimize inconvenience to the host site, only a handful of US government escorts will take part in the trials. A final trial observer will be a chemical industry expert who was involved with industry trial inspections for the Chemical Weapons Convention, thereby providing valuable perspectives from that experience. All trial participants will be screened for technical qualifications and conflicts of interest and required to sign the host site's confidentiality agreement.

The industry experts' proposed BWC trial inspection approach has no less than sixteen similarities with the practices that the U.S. Food and Drug Administration (FDA) employs. Where differences do exist, BWC trial inspections would in most cases be less burdensome than an FDA inspection. The group identified only two aspects of BWC trials that would be more onerous than FDA inspections, namely the size of the trial inspection delegation and the possible length of the on-site trial.

When a trial inspection concludes, the team will prepare a draft final report and the inspectors will share their findings with host site officials, both orally and in a concise, written report. An interactive feedback session will enable all trial participants to provide their observations and identify specific improvements to the proposed BWC monitoring strategies and techniques and for the conduct of future trial inspections. A series of post-trial briefings will relate the basic outcomes and lessons learned to U.S. government officials and lawmakers, bio-pharmaceutical trade associations, and appropriate international audiences.

In sum, the industry experts appreciate that a BWC trial inspection would be a burden, but it would not be an intolerable beast. Rather, they believe that the need to stem the proliferation of biological weapons makes it incumbent on the U.S. pharmaceutical and biotechnology industry, the U.S. government, and the international community as a whole to begin to resuscitate the BWC. Trial inspections are a necessary step in that direction. Should the proposed trials be conducted and demonstrate that inspectors can differentiate between legitimate commercial facilities and those masquerading as such, international negotiations should be swiftly restarted.

Organization of the Report

The first chapter of this report establishes the reasoning and methodology for the brainstorming sessions and provides an overview of the report. Chapter 2 contains an

abbreviated history of the international community's biological weapons nonproliferation efforts. Chapter 3 summarizes the industry experts' inspection hypothesis and specifies the types of facilities that would provide sound trial settings.

The bulk of this report is devoted to the components of the industry experts' BWC trial inspection plans, including the litany of logistical details outlined in Chapter 4. The fifth chapter lays out the activities that industry experts deemed appropriate to solicit the cooperation of potential host companies and properly prepare the trial inspection team. Chapter 6 details the on-site trial inspection plan, including protocols for several of the proposed monitoring activities. The seventh chapter discusses the post-inspection reporting and feedback processes. The report's concluding chapter features a discussion on the similarities between FDA inspections and the proposed BWC monitoring trial inspections and the industry experts' recommendations about how to move ahead with efforts to strengthen the BWC.

Chapter 1
Introduction

Discoveries emerging from pharmaceutical and biotechnology companies, research institutes, and university laboratories are rapidly and dramatically increasing the world's ability to recognize and combat diseases, remediate the environment, and increase harvests, among other things. At the same time, the potential for biotechnology to be misappropriated cannot be denied. Mankind has a decidedly unattractive habit of usurping commercial products for purposes of war and even harnessing science to create new weapons of war. For these reasons, the life sciences revolution that is underway is being regarded with some apprehension.[1] Human history is already tarnished with too many cases of governments mounting weapons programs to ready diseases for intentional use against plants, animals, and people.[2]

Currently, 167 countries are committed—on paper at least—to uphold the obligations of the Biological and Toxin Weapons Convention (BWC), which bans the development, production and stockpiling of biological weapons.[3] Unlike its chemical and nuclear counterparts, however, the BWC has no formal means of monitoring treaty compliance.[4]

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[1] For example, the use of phosgene and chlorine gas were among the battlefield atrocities of World War I. Scientists and policymakers are currently debating the dual-use nature of life sciences research and how to safeguard against man's worst intentions. The recent creations of a vaccine resistant mousepox virus and a synthetic polio virus have fueled concerns that not all scientific discoveries should be shared with the public. See Ronald J. Jackson, et al., "Expression of Mouse Interleukin-4 by a Recombinant Ectromelia Virus Suppresses Cytolytic Lymphocyte Responses and Overcomes Genetic Resistance to Mousepox," *Journal of Virology* 75, no. 3, (February 2001): 1205-1210; and Jeronimo Cello, Aniko V. Paul, and Eckard Wimmer, "Chemical Synthesis of Poliovirus cDNA: Generation of Infectious Virus in the Absence of a Natural Template," *Science* 297, no. 5583 (9 August 2002): 1016-1018. For more on the impact of biotechnology research on terrorism, see *Biotechnology Research in an Age of Terrorism*, Committee on Research Standards and Practices to Prevent the Destructive Application of Biotechnology (Washington, DC: National Academies Press, 2004).

[2] For more on the history of biological weapons, see *Biological and Toxin Weapons: Research, Development and Use from the Middle Ages to 1945*, Erhard Geissler and John Ellis van Courtland Moon, eds., Stockholm International Peace Research Institute Chemical and Biological Warfare Studies, no. 18 (London: Oxford UP, 1999).

[3] The BWC has 151 members and an additional 16 have signed, but not yet ratified, the treaty. *Meeting of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction*, BWC/MSP/2003/INF.2 (Geneva: 14 November 2003); See also the BWC website, www.opbw.org. Among the treaty members are several that the U.S. government has accused of having active biological weapons programs, including China, Iran, and North Korea. The Soviet Union ratified the BWC in 1975, but amassed the world's most fearsome bioweapons capability. Iraq, which signed the treaty in 1972 and finally ratified it in 1991 at the behest of the United Nations following the Gulf War, admitted in 1995 to having produced and stockpiled anthrax, botulinum, aflatoxin, and ricin. Syria, which has signed but not ratified the treaty, is also suspected of having a small-scale bioweapons research program. For more information on specific countries and citations, see the Nuclear Threat Initiative, Country Profiles, www.nti.org.

[4] The Chemical Weapons Convention (CWC) is the newest of the major nonproliferation treaties, having entered into force in 1997. The Organization for the Prohibition of Chemical Weapons (OPCW) regularly conducts routine inspections of member states' chemical facilities and has taken an active role in overseeing the destruction of chemical stockpiles in Russia, the United States, India, South Korea, and,

While the vast majority of pharmaceutical and biotechnology activity worldwide is devoted to peaceful scientific developments, the USSR and Iraq both concealed clandestine weapons programs under the guise of legitimate commercial activity. These circumstances highlight the vulnerabilities of the BWC. The cheating did not come to light as a result of treaty monitoring, and the BWC's members did not exact punitive measures against the violators.

The international community has made sporadic efforts to strengthen the BWC, but they often seem to take a backseat to steady, relatively strong campaigns to halt the spread of nuclear and chemical weapons. Jolts of concern about the maturing nuclear weapons programs in India, Iran, Pakistan, and North Korea concentrated international attention on nuclear nonproliferation, while the use of poison gas in the 1980s Iran-Iraq War gave momentum to the conclusion and entry into force of the 1997 Chemical Weapons Convention. The terrorist attacks involving anthrax in 2001 prompted a new wave of concern about biological weapons, particularly in the United States. Subsequently, a renewed sense of purpose appeared to be materializing around the world to address the problem of biological weapons proliferation.

Even though U.S. policymakers were talking the loudest about the threat of biological weapons, at the end of 2001 the United States recommended that talks to add a monitoring protocol to the BWC be disbanded, a move that shocked U.S. allies. Chapter 2 of this report relates the up-and-down saga of the international community's biological weapons nonproliferation efforts. In no small part due to U.S. actions, the international process has dwindled to only three weeks of technical and policy talks annually. In 2004, these talks addressed how to improve the BWC's current treaty monitoring arrangements. Discussion is restricted to the United Nations Secretary General's deployment of inspectors to investigate allegations of bioweapons use or suspicious outbreaks of disease. How to monitor the BWC's prohibitions against biological weapons development, production, and stockpiling was not open for discussion.

Experts from the U.S. pharmaceutical and biotechnology industry are not alone in recognizing the obvious gap between stated bioweapons proliferation concerns and international action to do something reduce this threat. Assertions have been bandied about for some time that the treaty is unverifiable or that the Chemical Weapons Convention's monitoring provisions can simply be transferred into a BWC setting. In addition to the dynamic and complex character of the life sciences and of the biopharmaceutical trade, claims that international inspections would reveal national security and proprietary business information have also frustrated those who contemplate

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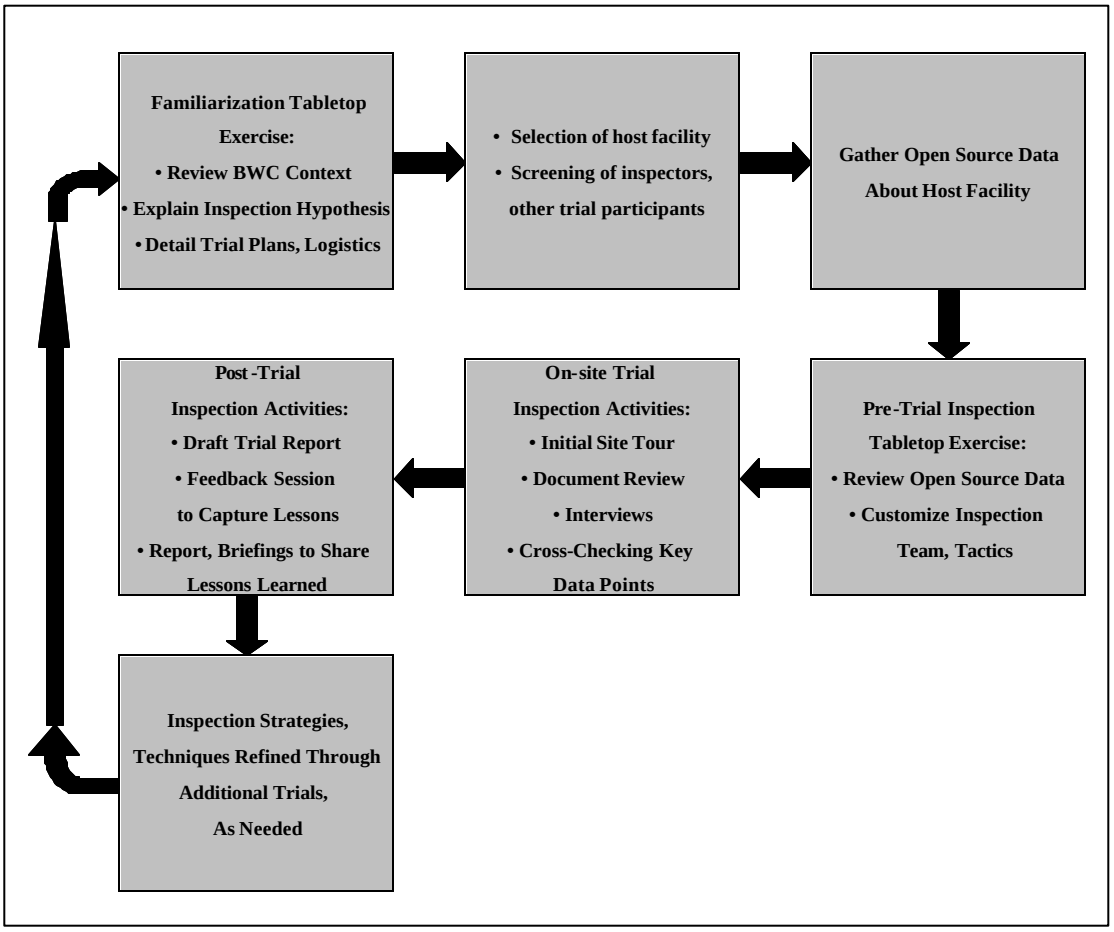
most recently, Libya. CWC members are also subject to more intrusive challenge inspections, although none have taken place. See the OPCW website, www.opcw.org. The Nuclear Nonproliferation Treaty (NPT) is the most universally adhered to nonproliferation agreement. Member states are required to declare their nuclear activities and submit to inspections by the International Atomic Energy Agency (IAEA). After Iraq and North Korea were found to be in violation of their NPT commitments in the early 1990s, the IAEA developed a strengthened safeguards system, which increased the inspectors' mandate and powers to detect clandestine nuclear activities. NPT members are strongly encouraged, but not legally obligated, to sign the Additional Protocol, which authorizes the more robust inspections. See the IAEA website, www.iaea.org.

creating mechanisms to monitor compliance with the BWC. Policymakers, industry officials, and the general public have accepted by rote that the BWC is "unverifiable" in the absence of actual and factual data. This state of affairs, when combined with the seriousness of the biological weapons threat, is untenable.

For that reason, a group of experts from the U.S. pharmaceutical and biotechnology industry have crafted a full-fledged proposal for monitoring the BWC at industry facilities, which have, as noted, been the favored place for governments to hide bioweapons programs. The experts in this group have over 330 years of industrial and scientific experience. Biographies for all of the experts involved can be found in Appendix 1. This group of industry experts has formulated very detailed plans, shown in skeletal form in Box 1, to field test whether their proposal is viable. They do so aware that Washington is not the only capital that would prefer to let this whole matter remain on the back burner. As scientists, however, they see a problem as something begging to be solved, not set aside until political convenience or some dire crisis again brings it to the fore.

Box 1: Stages of the Trial Inspection Process



Methodology and Organization of the Report

In March and June 2004, the Center for Strategic and International Studies convened two meetings with experts from the U.S. pharmaceutical and biotechnology industries as part of an ongoing series to draw on the technical expertise of industry scientists for the purposes of enhancing international biological nonproliferation weapons efforts.[5] These 2004 meetings built on previous sessions, held at the Henry L. Stimson Center, where industry experts developed their own formula for inspections to monitor the BWC's prohibitions at industry facilities and critiqued U.S. proposals tabled in 2001 as a substitute for a formal BWC monitoring protocol.[6] Chapter 3 of this report summarizes their original monitoring hypothesis.[7] In a nutshell, the industry experts argue that highly skilled inspectors using specific monitoring strategies and techniques should be able to discern legitimate facilities from those that mask illicit weapons activities. Their inspection hypothesis was the springboard for the trial inspection plans elaborated in this report.

In the 2004 meetings, the industry experts created detailed plans for trial inspections at U.S. biopharmaceutical facilities. Initially, the industry experts concentrated on how to monitor commercial manufacturing because they conceded that this would be a less demanding task than determining whether development activities were in compliance with the BWC. Then, the industry experts had a lengthy discussion about how to adjust both the hypothesis and the trial inspection plan for a biopharmaceutical development facility. Since the BWC does not ban research, the industry experts needed to define for monitoring purposes where research stops and development begins. In the end, they concluded that their hypothesis and plan apply to inspections of both manufacturing and development activities. However, they decided that at the outset separate trials should be held, some at manufacturing plants and others at development sites.[8] The industry experts intend these trials to be a reasonable test of the soundness of their proposed monitoring strategies and techniques, which they posit as a possible model for BWC verification of industry facilities.

Fully aware of the intricacies and dual-use nature of their science and industry, no member of the industry group looks at the task of monitoring the BWC through rose-colored glasses. To further inform their technical assessment of how to monitor the BWC, the industry experts had the benefit of a colleague from the chemical industry who represented the U.S. industry's views during the negotiation of the Chemical Weapons

[5] The first meeting was held on 8-9 March 2004 and the second was held on 17-18 June 2004, both at the Center for Strategic and International Studies in Washington, DC.

[6] See *House of Cards: The Pivotal Importance of a Technically Sound BWC Monitoring Protocol*, report no. 37 (Washington, DC: Henry L. Stimson Center, May 2001). This report also includes a proposal for how to monitor the BWC in research institutes and at universities, as well as the views of experts from research institutes and universities, defense contracting firms, and inspection veterans.

[7] Ibid., 49-84.

[8] Because of the complex nature of the activity being inspected at development facilities, the industry group expects trials at such sites to be less straightforward than in manufacturing facilities. The inspectors should find it easier to evaluate BWC compliance at manufacturing plants, which literally pride themselves on having an immutable process that is repeated from lot to lot.

Convention. U.S. chemical companies hosted trial inspections that were of tremendous assistance in helping the industry and U.S. policymakers determine that the proposed monitoring tools were effective and tolerable.[9] Commenting on the relative complexities of the nuclear, chemical, and biological weapons treaties, this individual said, "If you were to assign a numerical value representing the difficulties in monitoring these treaties, nuclear would be a one, chemical would be anywhere from 10 to 100, and biological would be from 100 to 1,000."[10] For scientists accustomed to searching for cures for intractable diseases, the difficulty of an endeavor is not a deterrent. The pharmaceutical industry experts believe the main ingredient missing is not the science, the strategy, or the tactics involved in BWC monitoring, but the willpower of U.S. policymakers and industry to press ahead with efforts to establish and enforce an international BWC monitoring regime.

The convictions of the industry experts are such that they propose the conduct of BWC trials at industry facilities as soon as possible. Holding such field trials would begin to bring the U.S. government itself into compliance with a 1999 law that both the Clinton and Bush administrations have ignored. The National Security and Corporate Fairness Under the Biological Weapons Convention Act requires the Executive Branch to conduct BWC inspection trials at industry sites, government installations, and academic institutions. The trials are to be followed by analysis of the monitoring benefits and risks that would accompany BWC inspections.[11] The industry experts view trials at U.S. pharmaceutical and biotechnology companies as educational tools to inform U.S. government policymakers and the biopharmaceutical industry. Ultimately, the lessons from U.S. industry trials should be shared with other BWC members.

The bulk of this report is devoted to the components of the industry experts' BWC trial inspection plans. The next chapter of this report, which reviews the history of efforts to strengthen the BWC, provides the context in which the industry group's proposals should be considered. Chapter 3 summarizes the industry experts' inspection hypothesis, states the overall goals for the trials, and specifies the types of facilities that would provide sound trial settings. When conducting a full field experiment, attention must be paid to a litany of logistical details, which are outlined in Chapter 4. The fifth chapter lays out the activities that industry experts believe should precede the arrival of trial inspectors at an industry facility, including several measures that the industry experts have added to ease the concerns of companies that might host trials. Chapter 6 describes the on-site trial inspection plan, including protocols for several of the proposed monitoring techniques. The seventh chapter details the post-inspection reporting process and the feedback process to capture the trial lessons and share them with U.S. government and international policymakers, industry representatives, and other interested parties. The

[9] For details of these trial inspections, see U.S. Congress, Office of Technology Assessment, *The Chemical Weapons Convention: Effects on the U.S. Chemical Industry*, OTA-BP-ISC-106 (Washington, DC: U.S. Government Printing Office, August 1993).

[10] Dr. William D. Carpenter, 8 March 2004. Dr. Carpenter has a Ph.D. in plant physiology and spent his 34-year career at Monsanto, where he retired in 1992 as vice president and general manager for agricultural technology. From 1978 to 1994 Dr. Carpenter represented the Chemical Manufacturers of America in the Chemical Weapons Convention negotiations.

[11] Public Law 106-113, 29 November 1999.

final chapter of the report provides a side-by-side comparison of the industry experts' proposed monitoring measures with those that the U.S. Food and Drug Administration employs. This chapter also contains the industry experts' observations about how to move ahead with efforts to strengthen the BWC.

Chapter 2
An Abbreviated History of the Biological and Toxin Weapons Convention

On 25 November 1969, President Richard Nixon renounced the use of biological weapons. This announcement built on and gave momentum to an ongoing British effort to develop a treaty banning biological weapons, which came to fruition on 10 April 1972.[1] On this day the United States, the United Kingdom, and the Soviet Union led a group of nations in signing the Convention on the Prohibition of the Development, Production, and Stockpiling of Biological and Toxic Weapons (BWC). President Nixon remarked at the signing that it was the "first international agreement since World War II to provide for the actual elimination of an entire class of weapons from the arsenals of nations."[2]

Over 30 years later, 167 countries have joined this treaty, but biological weapons are far from being eliminated. The pursuit of biological weapons continues among both state and non-state actors, although the BWC applies only to the former. The optimism that greeted the BWC's opening for signature disguised the treaty's greatest weakness: the BWC is devoid of effective, legally binding verification measures. Consequently, the BWC has been ridden with noncompliance. The potential of the BWC as a means of abolishing biological weapons still exists, but this potential will not be realized as long as the treaty lacks verification measures and is not enforced. To provide context for the monitoring hypothesis and trial inspection plans that U.S. biopharmaceutical industry experts propose in this report, this chapter details the turbulent history of the international fight against biological weapons, beginning with the BWC's entry into force.

The Early Years of the BWC

Although the 1925 Geneva Protocol had already outlawed the use of biological weapons and toxins,[3] the BWC went several steps further by banning the development, testing, production, and storage of biological warfare agents in quantities and types that have no peaceful, prophylactic, or protective justification. Article 1 of the BWC contains this broad prohibition, which is known in arms control and legal circles as the general purpose criterion. Article 1 of the BWC does not impede the legitimate use of agents for research and development of medicines, vaccines, and defense capabilities (e.g., gas masks, decontamination). Because the line between legitimate and prohibited activities is

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[1] The British introduced a draft treaty banning biological weapons in July 1969. The USSR and its allies responded by submitting their own draft treaty in September, which called for the elimination of both biological and chemical weapons. The United States supported the idea of separating the two, and Nixon's announcement strengthened the British position when Canada, Sweden, and the United Kingdom followed suit in declaring that they had no biological weapons or intent to produce them. See U.S. Arms Control and Disarmament Agency, *Arms Control and Disarmament Agreements: Texts and Histories of the Negotiations* (Washington, DC 1990): 129-130.

[2] Ibid., 131.

[3] The Geneva Protocol also outlawed the use of poison gas. However, fearing that states would not honor the agreement, the United States, the United Kingdom, France, the USSR and others stated that they would retaliate in kind if chemical or biological weapons were used against them. These reservations essentially turned the Geneva Protocol into a no-first-use treaty. Ibid.,10-12.

often a blurry one, determining compliance is inherently a difficult task.[4] For example, states could hide an offensive weapons program under the guise of legitimate commercial and defensive activities, which undermines confidence in the BWC.

Furthermore, Article III precludes states from helping others acquire biological weapons capabilities. Article XII stipulates that conferences be held every five years to review the operations and effectiveness of the BWC. Such review conferences have provided the forum for discussing problems stemming from the BWC's lack of verification measures.

Although the BWC does not have detailed on-site monitoring provisions, the BWC's architects did not completely ignore monitoring of treaty compliance. Rather, the treaty's drafters employed an approach typical of the era in which the treaty was created. Article VI of the BWC states that signatories can report suspected violations to the United Nations Security Council, which would investigate the accusation. However, the structure of the Security Council effectively limits the application of this provision. The five permanent members of the Security Council have veto power that could be used to block an investigation. Presumably, any member state accused of a BWC violation could turn to one of these five permanent members to secure such a veto. The only time that this mechanism has been partially triggered was in 1997, when Cuba raised charges that the United States used biological weapons against the island. Formal consultations were held with inconclusive evidence. No on-site investigation ensued, so the matter was never definitively settled.[5] So, in theory and in practice, Article IV has proved to be a poor compliance mechanism.

World events quickly revealed the BWC's inherent weakness. In 1979, less than five years after the treaty's entry into force, an accident occurred at a facility in Sverdlovsk, USSR causing dozens of people to fall sick and die of anthrax.[6] Soviet officials claimed that tainted meat caused the outbreak, but the United States suspected that the Soviet Union was not fulfilling its BWC obligations and that the outbreak was due to an accident at a military facility.[7] In this context, the First BWC Review Conference opened

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[4] To illustrate the point, a September 2001 *New York Times* article reported that U.S. defense researchers had developed a small bomb meant to disperse biological agents. The U.S. government claimed that the bomb was only used for biodefense research, but one former deputy of the Arms Control and Disarmament Agency noted that "in the eyes of the world, it's going to look like we've been clandestinely violating the treaty." See Judith Miller, "When Is a Bomb Not a Bomb: Germs Experts Confront the U.S," *New York Times*, 5 September 2001, A5.

[5] Cuba alleged that the United States had dispersed *Thrips palmi*, an insect that ruins fruit crops, from a crop duster in October 1996. In June 1997, Cuba requested formal consultations, which took place in August of that year. The United States claimed that the aircraft was heading towards Colombia for narcotics eradication when it came into close proximity with a Cuban airliner. The crop duster followed standard air safety procedure by indicating its location to pilots of the airliner by releasing smoke from a smoke generator to avoid a mid-air crash. See "Investigation of Allegations of U.S. BWC Violation Inconclusive," *CBW Chronicle* 2, no. 4 (Washington, DC: Henry L. Stimson Center, May 1998).

[6] For more on the anthrax outbreak at Sverdlovsk, see Matthew Meselson, et al., "The Sverdlovsk Anthrax Outbreak of 1979," *Science* 266, no. 5188 (18 November 1994). Sverdlovsk is now known as Yekaterinburg.

[7] *Soviet Noncompliance with Arms Control Agreements*, Special Report N.175 (Washington, DC: U.S. Department of State, Bureau of Public Affairs, 1 December 1982); *Soviet Noncompliance with Arms Control Agreements* (Washington, DC: U.S. Arms Control and Disarmament Agency, 1 February 1986).

in March 1980. Although concerns about verification were raised during the conference, the Final Declaration from the participating countries only noted the "importance" of Article VI of ensuring compliance.[8]

By the 1986 Review Conference, concerns about the BWC's lack of verification measures had increased. Advances in biotechnology were opening the possibility of genetically engineered weapons, including vaccine and antibiotic resistant agents.[9] At the Second Review Conference the participating states enacted a series of confidence-building measures (CBMs) meant to increase transparency between member states. Member states agreed to submit annual declarations on all high-containment facilities, any unusual disease outbreaks, the publication of pertinent research, and relative international contacts between scientists.[10]

Though well intended, the CBMs have largely been ineffective since few states have implemented them. At the turn of the century, only 75 states had ever submitted an annual report on CBMs, despite the fact that states can simply file a null declaration if they have no pertinent information to declare.[11] Although new CBMs were introduced at the Third Review Conference in 1991, to date, instead of reducing transparency, the existing CBMs have fostered the perception that nations do not take the obligations of the BWC seriously.

VEREX and the Creation of the Ad Hoc Group

When the Third Review Conference opened in 1991, verification and compliance were again high on the agenda. Given the lack of traction that CBMs were achieving, the international community opted to explore the feasibility of more rigorous monitoring measures. The mandate of the Ad Hoc Group of Verification Experts (VEREX) was to identify measures to determine whether a state was abiding by the BWC's general purpose criterion not to engage in activities with dangerous pathogens for other than peaceful or defensive purposes. In four meetings that stretched from 1992 to 1993, the VEREX group assessed over 21 measures for the compliance-relevant information each could or could not provide; its ability to separate prohibited activities from legitimate

[8] See the comments about Article VI in United Nations, *First Review Conference of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction: Final Declaration*, Document BWC/CONF.I/10, Part II (Geneva: 1980): 3.

[9] Aida Luisa Leven, "Historical Outline" in *Strengthening the Biological Weapons Convention by Confidence Building Measures*, Erhard Geissler, ed., Stockholm International Peace Research Institute, Chemical and Biological Warfare Studies, Report no. 10 (London: Oxford University Press, 1990): 8.

[10] United Nations, *Second Review Conference of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction: Final Declaration*, Document BWC/CONF.II/13/II (Geneva: 1986): 5-6.

[11] House Government Reform Committee, Subcommittee on National Security, Veterans Affairs and International Relations, Testimony of Donald A. Mahley, special negotiator for chemical and biological arms control, 13 September 2000.

ones; its ability to determine compliance; its financial, technical, and overall feasibility; and its impact on the industry and the protection of commercial proprietary information.[12]

After the final VEREX report was issued in 1993, a 1994 Special Conference concluded that "some of the potential verification measures would contribute to strengthening the effectiveness and improve the implementation of the Convention."[13] The Special Conference established an Ad Hoc Group to negotiate a legally binding instrument incorporating some of these measures.[14] This group met 24 times between 1995 and 2001, drafting a rolling text of prospective verification measures.[15]

By the time the Fourth Review Conference assembled at the end of 1996, two world events had underscored the need for monitoring compliance with the BWC. In 1992, Russian President Boris Yeltsin admitted that the Soviet Union had run a secret offensive biological weapons program.[16] Defectors from the USSR's bioweapons program revealed it to be formidable, having employed over 65,000 people at more than 50 facilities.[17] While Yeltsin issued a decree severely cutting back funds and personnel for the program, the United States and the United Kingdom wanted extra assurance that the program would be halted.[18] So-called trilateral inspections ended acrimoniously in 1994, however, and Russia has yet to open a handful of military biological facilities to outsiders.[19]

The USSR was not the only country to give the international community cause for concern about the BWC's viability. The end of the 1991 Gulf War resulted in the creation of the United Nations Special Commission (UNSCOM) on Iraq, mandated to oversee the eradication of Iraq's weapons of mass destruction. Iraq signed the BWC in 1972, but UNSCOM inspectors began to dig up evidence of noncompliance that finally compelled Iraq to admit in 1995 that it had produced and weaponized several biological

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[12] United Nations, *Ad Hoc Group of Governmental Experts to Identify and Examine Potential Verification Measures from a Scientific and Technical Standpoint: Summary Report*, Document BWC/CONF.III/VERX/8 (Geneva: 24 September 1993).

[13] United Nations, *Special Conference of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction: Final Report*, Document BWC/SPCONF/1 (Geneva: 19-30 September 1994): 2.

[14] Ibid., 3.

[15] For documents from each of the 24 sessions of the Ad Hoc Group, including the rolling text, see the Biological and Toxin Weapons Convention website at www.opbw.org.

[16] J. Dahlberg, "Russia Admits it Violated Pact on Biological Warfare," *Los Angeles Times*, 15 September 1992.

[17] See Ken Alibek with Stephen Handelman, *Biohazard* (New York: Random House, 1999).

[18] "Decree of the Russian Federation on Fulfilling International Obligations with Regard to Biological Weapons," Moscow, 11 April 1992.

[19] For more information on the Soviet biological weapons program and the trilateral inspections, see Anthony Rimmington, "From Military to Industrial Complex? The Conversion of Biological Weapons Facilities in the Russian Federation," Contemporary Security Policy 17 (April 1996): 81-112; David C. Kelly, "The Trilateral Agreement: Lessons for Biological Weapons Verification," Verification Yearbook 2002 (London: Verification Research, Training and Information Centre, 2002); *Toxic Archipelago: Preventing Proliferation from the Former Soviet Chemical and Biological Weapons Complexes* (Washington, DC: Henry L. Stimson Center, December 1999).

agents.[20] Two BWC signatories deliberately and grossly violated the treaty. However, the international community took no punitive action. The Fourth Review Conference convened within this context. Support for the Ad Hoc Group's negotiation of a monitoring protocol was strong, and the United Kingdom's representative noted that if the conference did not establish a verification regime prior to the end of the millennium it would be "failing in its duty."[21]

The Draft Protocol and the Fifth Review Conference

The Fourth Review Conference also urged the Ad Hoc Group to "intensify its work with a view to completing [the protocol] as soon as possible before the commencement of the Fifth Review Conference."[22] Developing a legally binding verification protocol was proving to be difficult for a variety of reasons, such as the dual-use nature of biological materials and equipment; the previously stated difficulty in distinguishing permitted defense activities from prohibited offensive ones; and the fact that small quantities of biological agents can be militarily significant.[23] As a result, when the rolling text of the protocol was put forth in 1997, it contained numerous bracketed sections that were still under dispute.[24]

Over the next four years negotiations continued on the areas of dispute and eventually the number of brackets began to decrease. By mid-2000, nations were submitting fewer working papers, and the focus had shifted towards the wording of the rolling text. In an effort to expedite the process, the chairman of the Ad Hoc Group submitted a composite text in March 2001, replacing the bracketed sections with compromise language designed to encourage agreement among state parties. This document set the stage for consideration of the draft protocol at the Fifth Review Conference.[25]

The negotiating endgame came to an abrupt halt in July 2001, when the United States announced that it would reject the draft protocol for three reasons. First, the document was based on traditional arms control measures that the U.S. government viewed as insufficient for establishing BWC compliance. The United States argued that the dual-

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[20] United Nations, *Report of the Secretary-General on the Status of the Implementation of the Special Commission's Plan for the Ongoing Monitoring and Verification of Iraq's Compliance with Relevant Parts of Section of Security Council Resolution 687 (1991)*, 11 October 1995) www.un.org/Depts/unscom/sres95-864.htm Security Council Resolution 687 also called on Iraq to ratify the BWC, which it finally did in June 1991. See United Nations Security Council Resolution 687, 3 April 1991.

[21] Statement of David Davis, Minister of State, Foreign and Commonwealth Office, to the Fourth Review Conference of the Biological Weapons Convention, 26 November 1996, quoted in "Fourth BWC Review Conference," *Disarmament Diplomacy*, no. 10 (November 1996).

[22] United Nations, *Fourth Review Conference of the Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction: Final Document*, Document BWC/CONF.IV/9,Part II (Geneva: 6 December 1996): 17.

[23] Jonathan B. Tucker, "The New BWC Process: A Preliminary Assessment," *The Nonproliferation Review* 1, no. 11 (Spring 2004): 29.

[24] The rolling text reached its peak in bracketed sections in November 1998, when it contained 3,200 areas of disagreement. Seth Brugger, "Prospects for Progress: Drafting the Protocol to the BWC," *Arms Control Today* 30, no. 4 (May 2000): 10.

[25] United Nations, *Protocol to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction*, Document BWC/AD HOC GROUP/CRP.8 (Geneva: 3 April 2001).

use nature of biological materials made verification by traditional means improbable, if not impossible. Second, the U.S. government stated that use of the inspection measures in the draft protocol would have revealed sensitive defense information and proprietary business data. Third, the United States argued that the draft protocol would open a window of opportunity for suspected proliferators like Iran to pursue the dismantlement of existing export controls, including the Australia Group. Such countries, according to the United States, would assert that any BWC member in good standing should be allowed full access to trade in dual-use biological materials and equipment. Accordingly, Washington saw the flaws of the draft protocol as systemic and decided against any further negotiations based on the proposed draft.[26]

At the Fifth Review Conference the United States presented alternative proposals for a monitoring protocol that focused largely on voluntary national measures, including penal legislation, scientific codes of conduct, and biosecurity controls.[27] At the tail end of the Review Conference, U.S. Under Secretary for Arms Control John Bolton took the entire international community by surprise by calling for the end of the Ad Hoc Group's negotiating mandate, effectively terminating negotiations for a legally binding verification regime for the BWC. Facing the dissolution of the Ad Hoc Group and widespread disagreement from other states, Review Conference Chairman Tibor Toth of Hungary suspended the meeting for a year.[28]

When the Conference reopened in November 2001, Toth proposed a new process involving a series of three annual meetings leading up to the 2006 Review Conference. The annual meetings would consist of a two-week meeting of experts, followed by a one-week meeting of policy specialists and diplomats. The aim of the meetings would be to "promote common understanding and effective action" in five areas: penal legislation, national biosecurity regulations, international response to biological weapons use and disease outbreaks, national disease surveillance mechanisms, and scientific codes of conduct. The proposal called for the first two areas to be discussed in 2003, the next two to be considered in 2004, and the final one to be broached in 2005.[29] Though several countries objected to this new process and its limited focus, the United States supported

[26] See John R. Bolton, under secretary for arms control and international security, "The U.S. Position on the Biological Weapons Convention: Combating the BW Threat" (Tokyo: 26 August 2002); Tucker, "The New BWC Process," 29.

[27] For more details on the U.S. proposals, see John R. Bolton, undersecretary for arms control and international security, "Remarks to the 5th Biological Weapons Convention RevCon Meeting" (Geneva: 19 November 2001). For an evaluation of these proposals by U.S. biopharmaceutical industry experts, see *Compliance Through Science: U.S. Pharmaceutical Industry Experts on a Strengthened Bioweapons Nonproliferation Regime* (Washington, DC: Henry L. Stimson Center, May 2001).

[28] "BWC: Review Conference Collapses," *Global Newswire*, 10 December 2001.

[29] United Nations, *Fifth Review Conference of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction: Final Report*, Document BWC/CONF.V/17 (Geneva: 19 November-7 December 2001 and 11-22 November 2002): 3-4.

the proposal. Realizing that the other alternative would be several years of inactivity, the BWC member states ultimately accepted this watered-down process.[30]

The New Intersessional Process

The first group of technical experts met in mid-August 2003 to discuss national legislation to criminalize biological weapons activities as well as measures to increase security for the transfer of and access to dangerous pathogens and toxins. Over 400 experts from 83 countries heard presentations from states on their national legislation and biosecurity measures. The mechanisms discussed ranged from decrees and executive orders to legislation in place and in draft.[31]

At the follow-up policy meeting in mid-November 2003, states disagreed about the purpose of the meeting. Some nations pressed for a final document that would provide voluntary guidelines for implementing national legislation and biosecurity regulations. Other states argued that national approaches covered too wide of a spectrum and in the weeklong period such guidelines would be impossible to develop.[32] The eventual result did not provide much reason for hope in the effectiveness of the intersessional process. A draft final report stressed "similar basic approaches" and "common principles" amongst the states' national legislation, but did not include guidelines to help states create national legislation. The final document from the 2003 meetings merely recognized the "value" of state cooperation in drafting national measures.[33] This "minimalist outcome" is notable for its systemic lack of harmonization and likely portends a web of differing national legislation. This outcome could provide an illusion of biological weapons security and nonproliferation.[34]

The August 2004 meeting of experts was held to assess international capabilities to investigate alleged biological weapons use and suspicious disease outbreaks. The delegations also discussed national means of disease surveillance, detection, diagnosis, and outbreak response. Officials from 87 BWC member countries attended, along with 450 international experts and representatives from the World Health Organization, the Food and Agriculture Organization, and the Organization for Animal Health. With the meeting format largely the same as 2003, various states parties gave statements and presentations. At the conclusion of the August 2004 meeting, the Chairman, Peter Goosen of South Africa, submitted a document detailing "considerations, lessons, perspectives, recommendations, conclusions and proposals drawn from the presentations,

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[30] The most significant protest to the new process came from the group of non-aligned states, including India, Iran, Pakistan, Mexico, and Cuba. Oliver Meir, "Bare-Bones Multilateralism at the BWC Review Conference," *Arms Control Today* 32, 10 (December 2002): 19-20.

[31] United Nations, *Meeting of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons: Report of the Meeting of Experts*, Document BWC/MSP.2003/MX/4, Part I (Geneva: 18-29 August 2003).

[32] Tucker, "The New BWC Process," 32.

[33] United Nations, *Meeting of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons: Report of the Meeting of States Parties*, Document BWC/MSP.2003/MX/4 (Vol. I), Part II (Geneva: 10-14 November 2003).

[34] Tucker, "The New BWC Process," 33.

statements, working papers and interventions."[35] This document was intended to give pertinent guidance to BWC members.

The results to date of the intersessional process appear to provide justification for its early critics. The meetings are too short, affording member states too little time to engage in meaningful discussions. Participants are failing to achieve the "common understanding and effective action" asked for by the Fifth Review Conference.[36] Even if more time were given for discussion of the five scheduled issues, the intersessional agenda is still too narrow. The agenda does not include other important topics, such as biosafety, oversight of genetic engineering research, and how to monitor BWC compliance related to the development, production, and stockpiling of biological weapons.

An important arms control accord in principle, the BWC without compliance monitoring and enforcement has proven little impediment to biological weapons proliferation. The U.S. government estimated that twice as many states were pursuing biological weapons capabilities in 1996 than were proliferating when the BWC entered into force in 1975.[37] Compliance concerns still hang over the BWC, which points to the urgency of continuing efforts to strengthen the treaty regime.

[35] United Nations, *Meeting of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons: Report of the Meeting of States Parties*, Document BWC/MSP.2004/MX/3, (Geneva: 11 August 2004); "Biological Weapons Convention Expert Meeting Concludes," *M2 Presswire*, 2 August 2004.
[36] United Nations, *Fifth Review Conference: Final Report*, 9.
[37] Statement of John Holum, director of the Arms Control and Disarmament Agency, to the Fourth Review Conference of the Biological Weapons Convention, 26 November 1996, quoted in "Fourth BWC Review Conference," *Disarmament Diplomacy*, no. 10 (November 1996).

Chapter 3
Framing Routine Treaty Compliance Inspections and Field Trials at Industry Facilities

The architects of the Biological and Toxin Weapons Convention (BWC) recognized something inescapable about the task of banning the transformation of disease into weapons of war. The dual-use nature of the materials, equipment, and the skills that scientists employ would make it very difficult to determine when someone had crossed the line from work to better mankind to the diversion of resources and capabilities for malevolent purposes. For that reason, the BWC prohibits activities that few would debate have breeched that line, namely the development, production, and stockpiling of biological weapons. Distinguishing hostile intent from legitimate research, however, is a different matter altogether.

The exclusion of research from the BWC's prohibitions meant that anyone who would eventually try to craft a monitoring regime for the BWC would not be asked to do the impossible. Still, the challenges involved in developing procedures to monitor BWC compliance are formidable. The first of these challenges is defining reasonable boundaries for what inspectors would monitor at complex industry facilities engaged simultaneously in several types of operations. The industry experts' straightforward discussion of what constitutes "development" is summarized in the next section of this chapter, followed by a review of the basic approach that the industry experts devised to monitor the BWC at industry facilities. This hypothesis debuted in an earlier report,[1] and the experts expanded and slightly revised it during their meetings in 2004. Next, the purposes and scope of trial inspections to test their hypothesis are explained. At the end of this chapter, the industry experts profile the types of facilities that could host field trials.

Getting a Handle on Development

Manufacturing is a term commonly understood to mean the activities associated with the making of a product, so enumerating what inspectors would monitor at industry production facilities is not all that difficult. "Development," however, is more nuanced than manufacturing. Development often goes hand-in-hand with research, hence the acronym R&D. Explaining how one category of activity blends into the next, one industry brainstormer said, "research is developing or optimizing the seed or organism. Development is taking that organism and trying to scale it up. From development, then you would go to manufacturing."[2] Whereas research can cover things as innocuous as assay development for protection from pathogens, development usually occurs in a pilot plant that can range from a couple liters in operating volume to 40,000 liters or more, which overlaps manufacturing volume levels. Therefore, biological or fermentation activities can exist in a continuum and can be difficult to assign to a particular category of

[1] See Chapter 4 of *House of Cards: The Pivotal Importance of a Technically Sound BWC Monitoring Protocol*, report no. 37 (Washington, DC: Henry l. Stimson Center May 2001).

[2] Dr. George Robertson, 17 June 2004. Dr. Robertson, vice president for the science and technology division of PDA, has over 30 years of experience in industry and biodefense and holds a Ph.D. in molecular biology.

facility. Moreover, all of this can take place under one roof, so to speak. One industry expert described a new pharmaceutical facility that was

> designed, built and validated to be able to actually make saleable material in case the manufacturing division couldn't make enough of it themselves. The site can run two campaigns and produce production material for the street out of an R&D facility. It's become a very gray zone between what's an R&D site and what's a production facility. This place put all of its research in the same building with the development and the scale-up simply because of the GMP [Good Manufacturing Practices] issues. It would be very hard to differentiate one from the other.[3]

In sum, activities can vary greatly among companies and facilities, so in reality inspections aimed at development could be applicable to industry research, R&D, and manufacturing facilities.

With this context in mind, the group of industry experts sought to define development, knowing also that the "R" side of R&D is not something that the treaty prohibits. For the purposes of BWC monitoring, therefore, some reasonable identifying characteristics are needed for the gray area between "R" and "D," not to mention between development and manufacturing. The bioindustry experts agreed that for BWC monitoring purposes, inspectors should concentrate on so-called scale-up activities and facilities working with certain dangerous pathogens. The term scale-up refers to the point later in the development stage at which scientists begin to reproduce materials in larger volume as a step toward full-fledged production. Scale-up activity takes place is a great many facilities.

To narrow the universe of facilities that might be considered for monitoring of development activity, the industry experts stated the first criteria that would qualify a facility to be inspected would be its work with a select agent. The U.S. Centers for Disease Control and Prevention requires all facilities and individuals to register "possession of biological agents and toxins that have the potential to pose a severe threat to public health and safety."[4] Likewise, any facilities or individuals possessing agents and toxins potentially harmful to animals or plants must report to the Animal and Plant Health Inspection Service under the U.S. Department of Agriculture.[5] Appendix 2 shows the U.S. select agent lists for humans, animals and plants. For the purposes of BWC inspections, facilities working with simulants of select list agents or with closely related organisms and/or toxins should also be inspected. A fair number of agents are on these lists, so inspectors might further prioritize facilities for inspection by taking into account the potency and infectivity of the agents/organisms at the facilities subject to inspection.

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[3] A Ph.D. scientist, this industry expert is also a senior industry manager who has published extensively and worked internationally.

[4] U.S. Centers for Disease Control and Prevention, Select Agent Program, www.cdc.gov/od/sap.

[5] U.S. Animal and Plant Health Inspection Service, www.aphis.usda.gov.

Next, the industry experts decided that additional specificity was needed regarding the level of scale-up activity deserving of the inspectors' attention. They settled on the threshold as the *volume* of a pathogen with which a facility is working, also referred to as the cell mass or cell count. In the development setting, however, a facility could produce continual nine-liter batches, which could, ostensibly, keep that site under an inspectorate's radar if fermenter size alone were used as the triggering factor. To ensure that inspections cover facilities engaged in a significant amount of development activity, the industry experts specified that the focus would be on the accumulated total, rather than on the individual batch size, of selected agents. Taking this approach a step further, the focus would be on the total accumulated cell mass, *however achieved*. The industry experts established a threshold for cell mass at 10^{13}, which equates approximately to the capacity of a 10-liter fermenter.[6] Facilities making this amount of a listed agent, toxin, or closely related organism—whether the material was developed in micro-liter or multiple liter batches—could be subject to an inspection. Facilities working with the equivalent amount of virus should also face inspections. Therefore, development activity that would be subject to inspection would be sites that work with a listed agent at an accumulated cell mass of $\geq 10^{13}$.

While these criteria might appear to confine inspections to biopharmaceutical companies, other types of facilities meet these criteria and are likewise theoretically capable of developing banned weapons. For that reason, the industry experts argue agricultural companies as well as food and enzyme production facilities should also fall under the purview of BWC inspectors. A BWC inspection regime would be deficient if it overlooked other facilities that had the exact same type of capabilities deemed worthy of monitoring at pharmaceutical and biotechnology sites.

Routine Inspection Hypothesis for Industry Facilities

Based on their technical expertise and industry experience, the group of experts created a hypothesis for how international inspectors might monitor BWC compliance at biopharmaceutical industry sites. This hypothesis applies to the routine inspection of industry facilities assumed to be engaged in legitimate commercial activity.[7] Except to state how a challenge inspection might be triggered out of a routine inspection, the industry experts did not address challenge inspections, which have been created for other treaties when allegations of cheating necessitate a more aggressive type of inspection. The industry experts' routine inspection activities fall into five main categories: pre-inspection data review, on-site tour, document review, interviews, and cross-checking key data points. The hypothesis also contains procedures for post-inspection reporting and response from the inspected company.

The Inspection Team

While the draft BWC monitoring protocol that died on the vine in the summer of 2001 postulated a four-person inspection team, the industry experts believe that the average inspection team size should be between six and eight members. The lowest number of

[6] For bacteria, a maximum of approximately 10^9 cells can be achieved in one milliliter of medium and 10^{12} in one liter.

[7] In the vernacular of the BWC, this type of inspection would be known as a non-challenge visit.

inspectors would be five, and, depending on the characteristics of the facility being inspected, the team could exceed eight specialists. Experience, rather than education, should be a more important criterion in qualifying inspectors, although all must hold at least a bachelor's degree in a pertinent scientific area. At a minimum, inspectors must have eight to ten years of experience in R&D, scale-up activities, operations management, commercialization, or multi-purpose consulting. The industry experts wanted all inspectors to receive additional training in auditing and in the psychology of conducting interviews. Depending on whether any of the inspectors spoke the host country's language, a sufficient number of technically/scientifically trained interpreters would accompany the inspection team. Legal and administrative staff would be on call at the inspectorate headquarters. Table 1 contrasts the industry group's proposal for a routine inspection with the provisions stated in the 2001 draft BWC protocol.[8]

Table 1: Comparison of the Industry Experts' Inspection Hypothesis with the 2001 Draft BWC Protocol

Monitoring Activity	Industry Experts' Inspection Hypothesis	Draft BWC Protocol
Data declaration	Minimal	Extensive[a]
Inspection team size	6 to 8	4
Advance notice of inspection	1 week	2 weeks
Inspection duration	Approximately 5 days, more time, if needed	2 days
Initial activity on site	Review of pertinent documents for on-site tour, followed immediately by tour	Host briefing, 3 hours
Duration of initial site tour	At least one day	2 hours
Other on-site inspection activities	Document review, interviews, examination of strain collection, final product sample, other samples as a last resort	Document review, interviews, sampling as a last resort request

[a] Under the 2001 draft BWC protocol, member states would have been required to provide detailed annual declarations about industry facilities that fit a certain profile centered around high-level containment and work with select agents. These declarations would have delved into equipment, personnel levels and publications, transfer of select agents to other facilities, media consumption, and size of the facility, among many other factors. For the declaration format, see pages 193-205 of United Nations, *Protocol to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction: Composite Text*, Appendix D, BWC/Ad Hoc Group/CRP.8, 3 April 2001.

[8] See United Nations, *Protocol to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction: Composite Text*, BWC/Ad Hoc Group/CRP.8 (Geneva: 3 April 2001).

The industry experts wanted a routine inspection to be conducted with a sufficient number of inspectors and enough time on site so that at the end, the team could walk away from the facility with no lingering questions. If the inspectors needed to extend their stay beyond five days, they would notify the company officials.

The industry experts were concerned that, more often than not, the inspection parameters incorporated in the draft BWC monitoring protocol would produce uncertain outcomes. If adequate resources are devoted to inspections, the inspectors will not be able to determine whether companies are performing legitimate business activities, or, far worse, covering up weapons activities. The industry group was wary of an inspection report that stated a facility had the wherewithal to develop and/or make biological weapons, but the inspectors were unable to conclude that the site was not doing so on the sly. In short, unless inspectors have sufficient time and resources to catch cheaters and give deserving companies a clean bill of health, inspections would not be worthwhile endeavors.

Pre-Inspection Preparations

Industry facilities will be obligated to provide the inspectors with only a minimum amount of information prior to the on-site visit. For manufacturing sites, this initial declaration will consist simply of the type and quantity of product(s) being made. Development facilities will inform the inspectorate of the type of R&D being conducted, as well as the type and quantity of warfare agents, simulants, closely related organisms and/or toxins on hand.

The crux of the industry experts' inspection methodology revolves around having the inspectors identify and reconcile, one way or the other, any activities or other aspects of the facility that are inconsistent with the standard scientific and professional practice for the activities that the facility declares. Given their industry experience, the inspection team would formulate its expectations based on a facility's data declaration, as well as their review of open source data before the inspection. While on site, the inspectors would pursue any inconsistencies that are revealed in greater depth, ideally until they are put to rest.

Prior to the on-site activities, the inspectorate will take the lead in assembling the core inspection team, who will start their investigation by collecting and analyzing a variety of open-source information. Publicly available materials such as staff publications in journals, on-line databases, patent estates, intellectual property portfolios, and news stories can help the inspectors shape their expectations for the facility and the regulatory environment in which it operates. With this information, the inspectors will be able to determine initial areas of emphasis for the on-site investigation and also bring additional specialists to the team as needed.

On-Site Inspection Activities

The industry experts crafted their monitoring procedures with corporate interests also in mind. The inspectors will sign confidentiality agreements with the inspected company and follow the company's guidelines for biosafety and product protection. The hosts will escort the inspectors for the duration of their time on site. Facility hosts will have the

right to inspect and control the use of all items the inspection delegation brings on site, although the industry experts requested a decidedly modest equipment kit for the inspectors. Their principal tools will be their eyes, ears, and minds, aided by pens, paper, and computers. Inspectors can request to bring cameras and take photographs, but the host companies will most likely balk at photographs. Other equipment the host will likely prohibit includes audio and video recording devices, personal digital assistants, and laptop computers equipped with wireless devices. Industry facilities have the option of providing the inspectors computers for their use.

According to the industry experts' hypothesis, the initial site tour should begin as soon as possible after the inspectors arrive at the facility. Prior to the initial tour, the company should provide the team with site-specific documentation (e.g., floor layout, as-built engineering diagram, and the piping and instrumentation diagram) so that the inspectors can quickly tune in to discrepancies between site records and site reality. The initial tour should be an interactive process, where inspectors chat with floor staff along the way and examine materials stored in freezers, refrigerators, and shelves. The inspectors should be particularly focused on inconsistencies related to the level of containment, types of equipment, types and quantities of biological material, waste handling system, and, if present, the animal facility. Overall, the inspectors should be concerned about whether a facility's capacity correlates with what the facility claims it is doing. The site would have the right to shroud a limited amount of sensitive equipment and attached piping, but should be prepared to explain to the inspectors why any items are concealed.

When the inspectors turn to the document review stage, they will examine a great deal of intentionally overlapping materials, with the view that anyone trying to hide bioweapons activities would leave an incongruous paper trail. At the same time, legitimate facilities should feel confident knowing that their records would help confirm their BWC compliance. The host site has the right to redact proprietary information unrelated to BWC compliance from documents. No documents would be allowed off-site without the written consent of the host, with the exception of a schematic of the process flow diagram, which will become part of the inspection record. Though the inspectors would certainly be thorough with their document review at a manufacturing plant, the industry experts predicted the inspectors would really pore over documents at a development facility. "There would be less walking, more reading in a development facility with multiple substances," said one industry expert.[9]

During the formal, structured interviews, the inspectors will press a variety of facility personnel through a systematic line of questioning. Although some companies coach their personnel in interview tactics so that they will avoid revealing confidential business information, such data is not the concern of the inspectors. Rather the inspectors would attend to such matters as whether the staff members know how to do their assigned jobs. An astute inspector should quickly detect an employee stumbling through a description of standard operating procedures to describe their duties. The industry experts agreed that a senior plant manager would be allowed to sit in on the interviews to assure the company

[9] Dr. George Robertson, Ph.D. in molecular biology and vice president for the science and technology division of the PDA, 17 June 2004.

that the inspectors are focused on determining BWC compliance, not digging for unrelated proprietary information.

Should the inspectors feel the need to check certain aspects of what they see and hear on site, they could conduct interviews with former employees, contractors, neighbors, and others off site who interact with the facility. The site being inspected would not be obligated to facilitate off-site interviews. If the inspectors exercise this option, they would have to factor in possible grievances, biases, or grudges that off-site individuals may hold against the company.

As they go about their duties, the inspectors should keep an eye out for unusual activities at the facility. Any number of things could be out of line with what the inspectors expect to see on site, such as:

- On-site housing, which could indicate that staff are kept under close watch;
- Mostly single workers, perhaps signaling that the work carries a high level of risk;
- An abnormally large number of controlled photocopy machines and shredders, which would be odd even for commercial plants that guard their information closely;
- Recent unexplained demolition activity, possibly indicating that the facility intentionally destroyed a banned capability;
- Medical facilities with an unusually high preparedness for employees' exposure to diseases;
- Excessive food or waste handling in the employee cafeteria, which could tip inspectors to restrictions in staff movement off site and possibly a greater number of people working at the facility than reported;
- Employees uncomfortable or unfamiliar with standard operating procedures, indicating they are not accustomed to performing the tasks associated with the declared activities; and,
- Employees with dermatitis, which could be a telltale sign that staff are working at a higher level of biosafety than declared.

No single one of these items would necessarily mean that a facility was covering up a weapons program, but such observations should certainly raise inspectors' suspicions of foul play at the site, particularly if host officials were uncooperative in answering inspectors' questions to clarify matters.

If the inspection team has been unable to resolve inconsistencies, then they will start digging deeper by cross-checking points of concern using the various inspection techniques. Should the host officials prove unwilling to provide inspectors with the documents, interviews, or on-site access that they request, the inspectors should inform the hosts officials of the inconsistencies and give them an opportunity to clarify matters. Inspectors should bump their concerns as high up the chain of command as possible, if needed. When the inspectors have exhausted all other options to sort out whether a

facility is masking something illegal, then the inspectors could turn to sampling as a last resort to get at the truth. Formal protocols for taking and analyzing samples should be based on pre-validated sampling and analysis techniques.[10] In normal circumstances, however, the industry experts agreed that only a final product sample would be part of a routine inspection. Real commercial manufacturers should have no problem providing a sample of their final product(s).

The industry experts agreed that the use of sampling to identify microorganisms would be the strongest tool to reveal any "smoking guns." A routine inspection crew could ask for in-process samples at either a manufacturing or a development site, but the host would likely refuse, citing the need to protect proprietary data. Practically speaking, therefore, in-process sampling would likely only take place during a challenge inspection, where the inspection team goes in at the behest of a BWC member that alleges cheating on the part of another.

Inspection Reporting and Follow-up

Once inspectors have assessed a facility's activities, they will prepare an inspection report to include their factual findings on items relevant *only* to compliance with the BWC. Should the inspectors conclude their on-site investigation with matters still in need of clarification, the draft inspection report would detail such issues. Host facility officials would be given the opportunity to provide additional data before the inspectors left the site. If that did not occur, the final inspection report would include a notice of any technical uncertainties or potential violation(s) at the facility. In most cases, the industry experts assessed, legitimate facilities would do everything in their power as quickly as possible to avoid the possible negative ramifications of being suspected of developing banned weapons.

The inspected facility will have 30 days from the receipt of the final inspection report to file a response plan that describes the steps that will be taken to clarify the remaining issue(s). Guided by the overall outcome of the investigation, the inspectors will examine the site's response, consult with their headquarters colleagues and with the inspected facility, and establish deadlines for the site to demonstrate that it has rectified the lingering concerns. Depending on the circumstances, the inspectors may decide that a follow-up routine inspection is needed to confirm that compliance has been established. Should a site fail to submit its plan for bringing its operations into compliance within the requisite 30 days, the industry experts declared such defiance as justification for another immediate routine inspection or even a launch pad for a challenge inspection if particularly serious issues were outstanding.[11]

The industry experts did not devise a complete challenge inspection hypothesis, but they began to frame three ways in which a challenge inspection could be triggered. The first, as just noted, would be the failure of the host site to file a plan to address outstanding

[10]For the industry experts' first discussion about sampling, see *House of Cards*, 69-73.

[11]Note that the industry experts did not expect the facility to have taken all of the steps outlined in its response plan within this initial 30 day time period. Depending on the issues involved, a facility might require some time to implement the plan.

issues. The second avenue would be if a BWC member alleged cheating based on their own intelligence information. The third route to a challenge inspection would be if the routine inspectors' concerns were so pronounced while they were on site that they informed the inspectorate that a challenge inspection team should be immediately dispatched to the site. The industry inspectors did not want to endanger inspectors by keeping them in a situation where it is clear that noncompliance is suspected and tensions are on the rise. They concluded that a more reinforced challenge inspection team would be needed to press the point with the facility operators.

The industry experts did not settle on how much, if any, notice should be given to a facility of a pending challenge inspection, but concerns have been voiced that a long notice would give a cheating site time to scrub away evidence of any suspicious activities before inspectors with a stronger challenge inspection mandate could arrive. "They can't clean it out completely," said one expert, "not with the tests that are available now with PCR [Polymerase Chain Reaction] and very sensitive enzymatic assays. It's not like chemicals; biologics are different. They leave footprints all over the place. Good luck cleaning all that out."[12] Another expert who had done work detecting damaged DNA agreed, saying, "You would be surprised what we were able to detect. We were shocked."[13] The Federal Bureau of Investigation has taken the lead in developing standard operating procedures for microbial forensics so that the evidence can withstand legal scrutiny.[14] Those working on developing sampling and analysis protocols for BWC compliance purposes can build on this research.

Once the routine inspectors believe that the situation warrants a challenge inspection, they should try to sample from appropriate points and establish a lockbox at the facility to store these samples in appropriate conditions. This lockbox would be sealed so that, if needed, the samples could be retrieved for analysis in the event that a challenge inspection team could not resolve matters.[15] If the host facility did not allow the routine inspectors to take such samples, then sampling would be a first order of business for the challenge inspection team upon their arrival.

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[12] Dr. Robert Goldberg, 8 March 2004. Dr. Robert Goldberg, Ph.D. in medical microbiology, has over 30 years of research and administrative experience in U.S. industry and at the National Cancer Institute. Polymerase Chain Reaction is a method used to quickly make multiple copies of DNA strands.

[13] Dr. Jennie Hunter-Cevera, 9 March 2004. Dr. Hunter-Cevera is president of the University of Maryland Biotechnology Institute with over 20 years of research and managerial experience in U.S. industry and research institutions and a Ph.D. in microbiology.

[14] Among the factors being addressed are proper sampling procedures, preservation of the sample so that its chemistry is not altered, chain of custody, and validated analytical tests. The Centers for Disease Control and Prevention, the National Institute for Standards and Technology, and the Food and Drug Administration are contributing to the development of these standards, so the industry should have reasonable confidence in them. These matters would all be reviewed with industry representatives to solicit their views.

[15] In addition, the industry experts raised the possibility of having the inspectorate instruct the facility to lockdown its operations until the arrival of the challenge inspection team. In the interim, the perimeter of the site might be monitored to track ingoing and outgoing materials, and intelligence satellites might be focused on the facility to watch its activities. While the industry experts raised these procedures for consideration, they did not work through the details. The industry experts noted that the Food and Drug Administration has on occasion resorted to lockdowns for severe regulatory violations.

The Purposes of Trial Inspections

The primary purpose for trial inspections is to test whether inspectors can tell the difference between legitimate industry facilities and covert weapons sites using the proposed inspection strategies and techniques. The secondary goal of trials is to educate various stakeholders in the policy formulation process, including the industry, U.S. officials, and other governments about what inspection strategies and techniques do and do not work in field conditions. As scientists, the industry experts understand that conclusive results should not be drawn from one trial. Rather, their strategy and techniques may need to be adjusted after an initial trial and additional field tests conducted until experimental data proves or disproves their hypothesis that it should be possible for inspectors to discern legitimate facilities from those masking prohibited activities.

During trial inspections, the inspection team will work from a site's declaration of development or manufacturing activity to verify that the facility is doing what it claims. Second, as Box 2 describes, the inspectors will try to confirm that the plant is not secretly producing biological agents or involved in illicit bioweapons-related activity on site. Finally, the inspectors will attempt to determine that the facility is not diverting significant and quantifiable item to other facilities involved in an offensive biological weapons program.[16]

Box 2: Goals for Trial Inspections of Industrial Facilities

Trial Inspection Goals
Inspectors are to confirm that the facility is: 1. Working with stated organism(s) and/or making stated product(s); 2. Not secretly developing or producing biowarfare agents on site; and, 3. Not diverting items to a covert biological weapons facility elsewhere

Recognizing that most U.S. companies will view trial inspections with a certain amount of skepticism, the group devised a walk-before-run strategy. Accordingly, the first manufacturing trial inspection will focus on monitoring the manufacturing process of only one specific product at the host facility, regardless of the other activities that may be taking place. The industry experts want companies to gain confidence in the viability of monitoring BWC compliance and the utility of trial inspections, so they recommended gradually increasing the difficulty of successive trials. In the initial trials, inspectors would focus on manufacturing or development activities, not both at the same time. As experience is gained, the industry experts believe the inspectors will come to understand what techniques work better in monitoring which type of activity and how long it should

[16] The items that could be diverted include virulent seed cultures, growth media, equipment, technologies, and personnel. In detecting diversion, the inspectors cannot just assert a hunch that something is missing. Rather, they must find evidence that the host facility is siphoning off a significant and quantifiable amount of one or more of these items.

take inspectors to monitor different types of facilities. Something of a composite inspection formula would emerge.

According to the hypothesis, each inspection and each trial will open with the assumption that the host facility is legitimate and intends to cooperate fully to demonstrate their compliance with the treaty. These assumptions are similar to the governing principles for industry inspections in the Chemical Weapons Convention.[17] The industry facilities hosting the trials are not in violation of the BWC, but at a certain point the inspectors' ability to detect cheating will need to be tested. In keeping with the walk-before-run strategy for trials, the industry experts also decided to rule out inserting scenarios into the initial trial inspections that would challenge the inspectors' ability to execute their duties.[18] The best of these scenarios mimic what could be expected to happen in real life, and the industry experts decided that such surprises should be woven into later trials.

Moreover, the industry experts stressed that the inspectors are there *only* to explore the feasibility of monitoring the BWC's bans against developing, producing, and stockpiling biological weapons.[19] In the extremely unlikely event that a trial inspection uncovered a BWC violation, the lead U.S. government official, likely to be from the State Department, should start immediate consultations with the company about how to rectify the circumstances and how to report the violation.[20]

As noted above, the secondary purpose of trial inspections is to serve as a learning experience for all sides—the host facility, the industry as a whole, the U.S. government, other governments, and others interested in developing a monitoring regime for the BWC. To minimize the intrusiveness of the trial on host facilities, however, the industry experts decided that actual trial participants will be limited to individuals with a specified role in the inspection process. Consequently, a wide variety of stakeholders—including

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[17] See Article VI; Annex of Implementation and Verification, Part II, paragraphs 38 to 41, 43, 45 to 5; Part VI; Part VIII; Part IX; and, Part X, paragraph 42 of the Convention on the Prohibition of the Development, Production, Stockpiling and Use of Chemical Weapons and on Their Destruction.

[18] The best "curve balls" are inspired by events that have occurred during actual international arms control inspections. Sample curve balls could include the host facility reporting that a certain area of the site is off limits because of a fire just prior to the inspection, a suspicious number of company managers or scientists conspicuously unavailable for interviews; medical records indicating an unusual number of illnesses or deaths in the vicinity, and facility hosts unable to find keys to unlock certain doors.

[19] The final report from a BWC inspection would contain *only* findings and violations pertinent to BWC compliance. If necessary, the inspectors would engage host officials in a private discussion after the trial to inform them verbally of potential U.S. regulatory violations (e.g., Occupational Health and Safety Administration) uncovered during the course of the trial.

[20] This set of circumstances is unlikely not because the inspectors would be incapable of finding a violation, but because the U.S. pharmaceutical and biotechnology companies are not serving as fronts for a covert weapons program. Moreover, no country has ever volunteered a report of cheating. The situation would be awkward for U.S. officials to navigate internationally since no international inspection agency exists where a violation would be reported. The U.S. government, as one of the BWC's depositary nations, might opt to notify other BWC members individually or issue a report of the violation and steps taken to bring the site into compliance at a meeting of BWC members, such as a BWC Review Conference. For a report on the first international discussion of a cheating allegation, Cuba's 1997 charge that a U.S. crop duster dispersed the pest *Thrips palmi* over the island, see Susan Wright, "Bioweapons Cuba Case Tests Treaty," *Bulletin of the Atomic Scientists* 53, no. 7 (November/December 1997): 18-19.

industry trade associations, executive branch officials, lawmakers, and their international counterparts—will not learn from first-hand participation in the trials. Instead, as Chapter 7 describes, these audiences would be briefed after the trials.

Profiles of Facilities to Host Trial Inspections

In developing plans for BWC trial inspections, the industry group articulated criteria that would identify the types of biopharmaceutical facilities that could serve as credible test beds for trials. These criteria differ somewhat for manufacturing and development activities, but they are both tied into biosafety levels, capacity, and work with dangerous pathogens.

The National Institutes of Health (NIH) categorizes biological organisms on a Risk Group scale, shown in Table 2. Each of the four Risk Groups has an associated level of biosafety driven largely by the availability of medical treatments for exposure to the organism in question. If medical treatments are widely available, then the disease can be worked with in biosafety level one, the lowest level of containment. The most dangerous organisms require the highest degree of physical containment, biosafety level four, to minimize the risk of working with such diseases. For large-scale facilities, the NIH mandates additional regulations to govern the handling of organisms and safeguards to deal with spills or accidental releases of the material. Facility operators must take into consideration "virulence, pathogenicity, infectious dose, environmental stability, route of spread, communicability, operations, quantity, availability of vaccine or treatment, and gene products such as toxicity, physiological activity and allergenicity" when determining the appropriate biosafety level for a particular activity with a particular organism.[21]

The industry group decided that the appropriate manufacturing facilities for trials should be large-scale sites working with class 2 organisms and above that are making biotechnology or pharmaceutical product(s) for commercial use. This categorization would also include facilities working with class 1 organisms that have been genetically modified to class 2 and higher. Class 2 agents are those "associated with human disease which is rarely serious and for which preventive or therapeutic interventions are *often* available."[22] NIH defines "large-scale" as research or production involving more than 10 liters of culture.[23]

For large-scale production, the highest level of physical containment allowed is biosafety level three. Although costs increase with the biosafety level, researchers can work in a

[21] National Institutes of Health, *Guidelines for Research Involving Recombinant DNA Molecules* (April 2002): 11. For a more detailed discussion on biosafety levels for large-scale facilities, see Appendix K of the NIH Guidelines.

[22] The NIH defines Risk Group 2 agents as those "associated with human disease which is rarely serious and for which preventive or therapeutic interventions are *often* available." Risk Group 3 agents "are associated with serious or lethal human disease for which preventive or therapeutic interventions *may be* available." Risk Group 4 agents "are likely to cause serious or lethal human disease for which preventive or therapeutic interventions are *not usually* available." Class 1 agents generally do not cause disease in healthy adults. Ibid., 36-42.

[23] Ibid., 11-12.

higher level of containment than the organisms require. In other words, a biosafety level three laboratory could actually be working with a class 2 organism such as *Bacillus anthracis*.

Table 2: An Illustrative Listing of Microorganisms in the NIH Risk Groups [a]

Risk Group 2 Treatment is *often* available	**Risk Group 3** Treatment *may* be available	**Risk Group 4** Treatment is *not usually* available
Bacteria *Bacillus anthracis* (anthrax) *Clostridium botulinum* (botulism) *E. coli* *Salmonella* **Parasites** *Cryptosporidium* *Giardia* *Plasmodium* (malaria) **Viruses** Dengue Hepatitis A, B, C, D, and E Influenza Measles Polio Rabies Chickenpox	***Bacteria*** *Brucella* (brucellosis) *Yersinia pestis* (plague) ***Viruses*** Rift Valley fever Japanese encephalitis Yellow fever HIV	***Viruses*** Ebola Marburg Machupo Crimean-Congo hemorrhagic fever

[a] National Institutes of Health, *Guidelines for Research Involving Recombinant DNA Molecules*, Appendix B (April 2002): 36-42.

The industry group's criteria for a manufacturing trial, summarized in Table 3, make a significant pool of potential sites theoretically available as test beds. For example, every large pharmaceutical company in the United States has at least one large-scale manufacturing plant handling class 2 or greater organisms. Many biotechnology firms, as well as universities, also have class 2 production facilities.

A large number of U.S. facilities also meet the criteria established for development activity trials. The industry group determined the primary triggers to be a facility with scale-up capability that works with one or more agents on the select lists of human, plant, and animal biological agents; with simulants of these organisms; or with closely related organisms and/or toxins. The scale-up capacity would be the aforementioned accumulated cell mass or cell count of 10^{13}, however achieved.[24]

[24] As noted earlier, this capacity basically equates to a 10-liter fermenter. The same cell mass of virus would also be covered.

Table 3: Characteristics of Industry Facilities Suitable for U.S. Trial Inspections

Manufacturing Trial	Development Trial
• Risk Group 2 or higher organisms • Large-scale production capacity	• Working with listed agents, simulants, closely related organisms, and/or toxins • Cell mass/cell count greater than 10^{13} however achieved; equivalent for viruses

With the stipulated criteria, the industry group noted that several types of facilities could be test beds for BWC monitoring of development activities. Types of sites likely to qualify include pharmaceutical companies, animal vaccine development facilities, government contractors, government laboratories, universities, and biotechnology firms working through grants under the NIH Small Business Innovation Research program.[25] The most attractive site for a development-oriented trial would be an industry facility, but if U.S. companies did not agree to host trials, then similar sites could be found at government laboratories and universities.

[25] This federal program supports small U.S. businesses that are conducting commercially viable R&D. For more information, see the NIH website, http://grants.nih.gov/grants/funding/sbirsttr_programs.htm.

Chapter 4
Trial Inspection Logistics

Soliciting volunteers is never an easy business, even when altruistic objectives are involved. A handful of U.S. companies can benefit the U.S. biopharmaceutical industry as a whole, the U.S. government, and international peace and security by helping to determine whether compliance with the prohibitions of the Biological and Toxin Weapons Convention (BWC) can be established at industry facilities. Obviously, tests of the inspection hypothesis summarized in Chapter 3 cannot proceed without the cooperation of some U.S. pharmaceutical and biotechnology companies. Therefore, the industry experts have fashioned their trial inspection plans to lessen the burdens on host facilities while still enabling credible tests of the ability to monitor the BWC at industry sites.

Working from their hypothesis for real-world inspections, the experts loosened the reins somewhat to create a more hospitable trial inspection environment. This chapter describes the procedural and operational backbone for trial inspections, reflecting the group's aim to accommodate the reservations that they, as industry insiders, could anticipate. After a discussion of the trial inspection timeframe and team composition, the chapter describes the additional members of the inspection delegation and the process for screening all trial participants. Other logistical matters are addressed at the end of this chapter.

Inspection Duration

Given the number of activities that inspectors must undertake to confirm whether a facility is engaged in its stated purpose(s), the industry group had some concerns about how long a trial inspection could last. A two-day exercise would be superficial and insufficient to test whether cheaters could really be parsed from good guys, whereas two weeks on site would be overkill, not to mention out of line with their original inspection hypothesis that an inspection lasting five days should enable the team to accomplish its goals. This timeframe could vary, however, depending on the size and complexity of the facility to be inspected. Recalling the adage that "fish and visitors stink in three days,"[1] the bio-industry experts agreed that the ideal timeframe for trial inspections of manufacturing and development facilities would be the same as their estimation of what a real inspection would require, five days.

These five days would encompass the entirety of the on-site inspection activities, from the initial tour to cross-checking to resolve any abnormalities or inconsistencies found by inspectors. Pre-inspection and post-inspection activities could involve additional time on the part of host facility personnel, but would not require inspector access to working areas of the facility or records.

[1]Dr. George Pierce, 8 March 2004. With a Ph.D. in microbiology, Dr. Pierce has over 20 years of experience in the U.S. pharmaceutical industry and is currently a professor of applied and environmental microbiology at Georgia State University.

Recommended Expertise for the Inspection Teams

The group decided that someone deeply knowledgeable about the manufacturing or development process should head the inspection, a "super" team leader of sorts. The type of individual who would have the range of experience and knowledge needed—from line and bench activities to front office operations—might be a former company vice-president with a relevant scientific background. In addition to having the technical industry experience, the team leader should be a strong spokesperson and tough negotiator with a healthy smack of skepticism. The team leader would be responsible for the overall conduct of the inspection, delegating duties as necessary, and would serve as the primary interface between the inspection team and host facility.

Table 4 shows the recommended inspection team composition, which differs for manufacturing and development facilities. Total team strength should be seven or eight, but could go higher or be as low as five, depending on the nature of the inspected site. Core team members are considered integral to performing a thorough inspection. Aside from the team leader, both teams would have an industrial microbiologist and a facilities engineer. The industrial microbiologist should have expertise in bacteriology, virology or infectious disease, depending on the work being conducted at the facility. Of the decision as to what type of industrial microbiologist to bring along, one industry expert noted that "the infectious disease person is going to have a nose that is differently trained than [a standard] industrial microbiologist, better for looking at those off-beat products or those off-beat experiments."[2] The facilities engineer would hone in on the ventilation system, "getting up in the mechanic space and kicking the HVAC and making sure there aren't HEPA filters on the exhaust."[3] Inspection teams headed for manufacturing sites might include one individual who would be knowledgeable in regulatory/quality control/instrumentation/validation, or the basic characteristics of a manufacturing site could dictate that as many as four different people would be needed to cover these areas. The core team of inspectors examining development activities would be rounded out by a quality assurance specialist, who would feel right at home and be very effective at examining records.

Depending on what the facility declares it is doing and what information can be gleaned from the pre-inspection open source data collection and analysis, the inspection team leader might expand the core team with additional expertise. An infectious disease specialist, for example, would be added to the team inspecting a manufacturing plant if the data collection revealed an unexplained or otherwise odd disease outbreak in the vicinity of the plant. At a development facility, a toxicologist, biochemical engineer, veterinarian, and chemist are among the specialties that might flesh out the inspection team. Table 4 lists the additional areas of expertise that industry experts believe the team

[2]Dr. Robert Goldberg, 17 June 2004. Dr. Goldberg, Ph.D. in medical microbiology, has over 30 years of research and administrative experience in U.S. industry and at the National Cancer Institute.

[3]Dr. George Robertson, 17 June 2004. Dr. Robertson, vice president for the science and technology division of PDA, has over 30 years of experience in industry and biodefense and holds a Ph.D. in molecular biology. HVAC stands for heating, ventilation and air conditioning system, while HEPA is an acronym for high efficiency particulate arresting filters.

leader should enlist, as needed, to ensure that the inspection is tailored to the site in question.

Table 4: Composition of the Inspection Teams

Core Inspection Team	
1. Team leader (expert in one or more of the relevant disciplines) 2. Facilities engineer 3. Industrial microbiologist (e.g., virologist, bacteriologist, infectious disease specialist)	
Manufacturing Facility Core Team	**Development Facility Core Team**
4. Biochemical or bioprocess engineer 5. A specialist with either regulatory, quality control, instrumentation, or validation experience	4. Quality assurance expert
Possible Auxiliary Specialists	**Possible Auxiliary Specialists**
6. Regulatory expert 7. Quality control expert 8. Instrumentation expert 9. Validation expert 10. Infectious disease specialist	5. Quality control expert 6. Instrumentation expert 7. Validation expert 8. Veterinarian 9. Toxicologist 10. Chemist 11. Biochemical engineer

The U.S. Government Escort Component

Implementing inspections under an international arms control treaty necessarily involves the U.S. government, which traditionally serves as the official interface between international inspectors and U.S. sites to be inspected. The State, Commerce, and Defense Departments have played leading roles in this interface process. For example, the State Department houses the office in charge of implementing the Chemical Weapons Convention (CWC) and in that capacity transmits to the CWC's international inspectorate in The Hague the data that the Commerce Department collects from U.S. chemical facilities meeting certain criteria. For its part, the Defense Department has a trained cadre of escorts who accompany international inspectors throughout their stay in the United States.[4] The size of the delegation involved in an inspection at an industry facility can balloon with U.S. government representatives. As many as two U.S. escorts normally accompany each CWC inspector.

While appreciating a need for a U.S. government role in both real and trial inspections, the industry experts also sought to design a trial process that would pose the least

[4]The State Department's Office of the National Authority, the Commerce Department's Bureau of Export Administration, and the Defense Threat Reduction Agency's On-Site Inspection Directorate are the three principal entities leading the U.S. government's implementation of the CWC. The Defense Threat Reduction Agency subsumed a free standing Defense Department agency formed in the late 1980s to oversee implementation of early treaties involving inspections. For a history of these activities, see Joseph P. Harahan, *On-Site Inspections Under the INF Treaty* (Washington, DC: On-Site Inspection Agency, U.S. Department of Defense, 1993); Joseph P. Harahan and John C. Kuhn, III, *On-Site Inspections Under the CFE Treaty* (Washington, D.C.: On-Site Inspection Agency, U.S. Department of Defense, 1996).

possible burden on sites that might host trials.[5] Industry experts explained that companies that host trial inspections will feel compelled to assign a corporate escort to each and every outsider that steps on their premises, even if said individuals are from the U.S. government. Therefore, the industry group's rule of thumb guiding the inspection delegation is "essential personnel only" to lessen the corporate staff time that a trial consumes.

In hopes of promoting industry's confidence and partnership, the industry group set a limit on the number of U.S. government escorts that would participate in a trial inspection. No more than six U.S. government officials would be involved in the first trial or two, and those who do take part will go through a selection process. The industry group decided that government escorts should be knowledgeable about the BWC, the inspection process, or the industry and its sciences. The screening criteria that apply to both inspectors and U.S. government escorts are discussed later in this chapter.

Having set this numerical limit on U.S. government participants, the industry experts nonetheless stipulated the trial process should benefit the U.S. government's learning curve and policymaking process. The group did not rule out larger U.S. government participation in later trials. In the meantime, the U.S. government officials who do participate will be responsible for disseminating the lessons learned from the trial to their respective agencies, working from the text of the final trial report. According to one industry expert who has worked closely with both industry and government, "the only way the government is going to benefit is by sending the best people that can gain that experience, so they could do the education or workshop procedures after" the trial.[6]

Due largely to its status as the traditional liaison in international activities of this nature, the industry experts believed that a State Department official should lead the escort team. The industry group concurred that officials from the following branches of government would be more likely to have applicable knowledge and experience and therefore would be viewed by prospective host companies as adding to the integrity and credibility of the inspection: the Department of Defense, preferably someone from the Defense Threat Reduction Agency and/or a current or retired official from the U.S. Army Medical Research Institute of Infectious Diseases; the Centers for Disease Control and Prevention; and the National Institutes of Health. The industry experts stated that an official from the National Institute of Standards and Technology of the Department of Commerce might be recruited to escort inspectors during manufacturing trials, but did not include an official from there as a potential escort during trials at development facilities. The obvious part of government missing from that equation is the Food and Drug Administration (FDA). Although a retired FDA official might serve as an inspector, the

[5]As one brainstormer emphatically stated, "Every member of that team should have a pre-assigned function. It shouldn't be government people walking around and getting in the way of people that are trying to do their job. Having worked in government and in industry, what I'm concerned with is walking in with a cast of thousands." Dr. Robert Goldberg, Ph.D. in medical microbiology with over 30 years experience in research and industry, 8 March 2004.

[6]Dr. Jennie Hunter-Cevera, 8 March 2004. Dr. Hunter-Cevera is president of the University of Maryland Biotechnology Institute with over 20 years of research and managerial experience in U.S. industry and research institutions and a Ph.D. in microbiology.

industry experts agreed that the involvement of a current FDA official as an escort would likely scare off industry sites that might consider hosting a trial.[7]

Additional Members of the Inspection Delegation

Inspection Ombudsman

Mindful of the need to limit the total number of inspection participants, the industry experts voted to expand the size of the inspection delegation slightly to enhance the evaluation of the inspection process. First, the industry experts wanted trials to be as even-handed as possible. Second, the group wanted trials to have the benefit of evaluation from very skilled outside experts.

To foster a truly independent assessment of the events that transpire, the group decided that trial inspections should have an ombudsman. The ombudsman would have full access to all inspection activities, including sitting in on the inspectors' meetings. The industry experts agreed that the ombudsman should be a systems analyst with sufficient experience to analyze the integrity and effectiveness of each phase of the inspection. If need be, the ombudsman would also act as a referee who could "be used by either side to adjudicate or resolve issues on site."[8] At the conclusion of the trial, the ombudsman would present a separate report on the integrity and effectiveness of the trial, as well as on the conduct of the inspection team, the government escorts, and the host site. The ombudsman would also present recommendations to improve future trials.

Chemical Industry Observer

Another trial participant would be an individual from the chemical industry who was involved with the CWC negotiations and associated trial inspections of chemical facilities. The group decided that despite the greater complexities of verifying the BWC, many valuable insights could be gained by having such an individual observe the trial through the lens of their prior experience. For example, if something went awry, this person could relate how chemical industry assessed and resolved the problem. Conversely, the industry expert might offer cautions borne of experience when everything in a trial has gone smoothly. In the post-trial feedback session, this individual would not be required to file a separate report, but would be encouraged to comment on the trial and offer recommendations. Of course, both the chemical industry observer and the ombudsman would go through the same rigorous screening process as inspectors and escorts.

Selection of the Inspection Delegation

In choosing inspectors for the trial(s), the industry group intends to assemble a "dream team" from the biopharmaceutical industry, academics with industry experience, and retired government officials. This combination of expertise will provide "balance and

[7] FDA officials are legally obligated to report any FDA-related infractions, which could lead to additional inspection(s) of the facility. Given that U.S. companies are already subject to routine FDA inspections, the group agreed it would be untenable to have current FDA officials involved in trials.

[8] Dr. George Pierce, professor of applied and environmental microbiology at Georgia State University and 20-year plus veteran of U.S. industry, 17 June 2004.

different perspectives" to enable the inspection team to fulfill its mandate.[9] According to the hypothesis, experience should outweigh education when it comes to selecting the inspectors. The industry experts would accrue a pool of potential inspectors by soliciting names from industry contacts and relevant life sciences associations and professional societies. Certain government agencies could also be asked to recommend recently retired colleagues, and the National Science Advisory Board on Biosecurity might also be an avenue to candidate inspectors.[10]

To winnow down the pool of names, prospective inspectors will be contacted and asked to go through a two-tiered screening process regarding their qualifications and any potential conflicts of interest with the site(s) being inspected. For the initial trials, the industry experts recommended that all participants be U.S. citizens, but opened the possibility that international inspectors and/or observers could be invited to take part in subsequent trials. Trial organizers would screen suitable candidate trial inspectors in consultation with industry experts.

While the information candidates must submit is extensive and could potentially deter some qualified individuals from applying to be inspectors or observers, the group decided that the more the trial facilitators know of their participants, the better the chance of having the best people involved and the higher the probability of successful partnerships with host sites. On the technical side, the information that trial participants must provide includes their education, work history, military background, experience with select pathogens, professional activities, accomplishments, and affiliations. Conflict of interest statements include personal or financial connections with the host company, consulting relationships, affiliations, criminal record, and travel history. Box 3 lists the complete set of information required to determine candidate inspectors' suitability.

Box 3: Screening Criteria for Candidate Inspectors and Escorts

Technical Vetting	Conflict of Interest Vetting
Curriculum vitae and supporting information and statements that include: 1. Basic background data: • Name • Prior name(s)/aliases • Date of birth • Nationality • U.S. citizen • Address	Conflict(s) to be stipulated, including, but not limited to: 1. Agent of foreign power 2. Potential financial interest in host entity 3. Financial disclosure, including other income sources 4. Consulting relationships 5. Criminal record[a] 6. Disbarment, investigation, and/or misconduct related to receipt of federal funds[b]

[9] Dr. Jennie Hunter-Cevera, Ph.D. in microbiology and president of the University of Maryland Biotechnology Institute, 8 March 2004.

[10] The National Sciences Advisory Board for Biodefense was established to "provide advice to federal departments and agencies on ways to minimize the possibility that knowledge and technologies emanating from vitally important biological research will be misused to threaten public health or national security." Up to 25 voting members will serve on the board, with areas of expertise including the life sciences, public health, national security, and law enforcement. NIH manages the board. See the board's website, www.biosecurityboard.gov.

Box 3: Screening Criteria for Candidate Inspectors and Escorts (continued)

Technical Vetting	Conflict of Interest Vetting
• Emergency contact • Education • Current occupation/employer • Work history • Military experience (biodefense, security clearance) 2. Relevant professional experience: • Publications • Presentations (last 10 years) • Patents (U.S./Patent Cooperation Treaty)[c] • Professional society memberships • Honors/awards 3. Ability/authorization to sign or be bound by secrecy/nondisclosure agreement 4. Relevant experience with select agents: • 42 Code of Federal Regulations (CFR), Part 73[d] • 7 CFR and 9 CFR[e] 5. Foreign language capabilities 6. References	7. Social security number 8. Countries visited in last 10 years 9. Visas to visit foreign countries

[a] A criminal record, particularly if the crime carries a prison sentence of 12 months or more, would disqualify candidates from participating in a trial inspection.

[b] Anyone that has been banned from receiving NIH funding would be ruled ineligible.

[c] The Patent Cooperation Treaty allows an inventor to apply for a patent in several countries through a single application. For more information, see the website of the U.S. Trade and Patent Office at www.uspto.gov.

[d] 42 CFR, Part 73 established the requirements for "possession and use in the United States, receipt from outside the United States, and transfer within the United States, of select agents and toxins" deemed harmful to humans. The Department of Health and Human Services established these regulations in response to the Public Health Security and Bioterrorism Preparedness and Response Act of 2002. *Federal Register*, Department of Health and Human Services, Part IV, 67, no. 240 (13 December 2002).

[e] 7 CFR and 9 CFR established the requirements for "possession, use, and transfer of biological agents and toxins that have been determined to have the potential to pose a severe threat to both human and animal health, to animal health, to plant health, or to animal and plant products." The Animal and Plant Health Inspection Service of the Department of Agriculture established these regulations in response to the Agricultural Bioterrorism Protection Act of 2002. Federal Register, Department of Agriculture, Part V, 67, no. 240 (13 December 2002).

The industry experts did not recommend such extensive screening criteria lightly. Numerous items received lengthy discussion. Some items would provide insight for certain candidates (e.g., publications, travel visas), whereas others would not.[11] Although wary about privacy issues associated with asking for candidates' social security numbers, they are required in standard job applications and would be necessary for conducting credit checks and checking tax records. Worried that overly broad conflict of interest parameters could potentially eliminate otherwise qualified inspectors, some of the industry experts advocated just asking candidates to list any potential or perceived conflicts of interest with the host site.[12] Eventually the group concluded that a wider approach would serve the integrity of the inspection better.[13] A couple of questions may prompt the candidates to identify some areas of possible concern, but candidates may unintentionally fail to pinpoint some conflicts. "You have to remind some executives that they sit on boards of directors of other companies," quipped one industry expert, who went on to note that some candidates might not connect the ownership of their company to their qualification as an agent of a foreign power.[14] The industry experts aimed to simplify the list of items that candidates should disclose because they viewed federal and state conflict of interest forms as nightmarish.

Logistics and Visitor Controls

Industry sites are quite accustomed to having regulatory inspectors, so the group of experts asserted that very little extra preparation would be needed on the part of a host facility to participate in a trial. Corporate personnel are already trained and procedures are already in place to host visitors and safeguard site secrets, so host officials should be able to work from existing plans and capabilities. The host sites would have sole responsibility for internal communications and informing facility personnel of the unusual nature of the exercise to occur.

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[11] For example, former government personnel may have security clearances, but that is not likely to be the case for industry personnel. Front office executives may not have published in many years, but publications and presentations can still help validate participants' backgrounds. Travel visas may help the trial organizers to identify who the candidates may have met while traveling overseas.

[12] One industry expert pointed to the FDA to illustrate the concern. "They have eliminated some of the best expertise in the business because of their huge conflict of interest criteria. They're having trouble trying to qualify people to sit on the review panels at the FDA now. So you have to be a little bit careful. You don't want to eliminate the best people by being too rigid about these whole conflict of interest values." Dr. Robert Goldberg, Ph.D. in medical microbiology with over 30 years experience in research and industry, 17 June 2004.

[13] According to one expert, "Whenever conflict of interest is addressed, the door should be opened as wide as possible. Whenever you ask for specifics, you then have to judge whether there is a conflict. It is much better to say to the person, 'Here is what you are going to be doing. Do you have any financial or any other conflict that may influence this, personal or anything else?' They write it down. Then they have identified a conflict, but that may not be the only conflict." Dr. Claude Nash, 17 June 2004. Dr. Nash, Ph.D. in microbial genetics, is vice president of research and development for the University of Maryland Biotechnology Institute, founded his own biotechnology company, and has over 30 years experience in industry.

[14] One participant noted, "Technically speaking, certain U.S. companies are not U.S. companies. They are actually controlled by foreign powers. A company owned by a British holding company in the United States is basically a part of a foreign power. Once this is declared, it is not an issue. It is an issue if you don't declare it." Dr. George Pierce, professor of applied and environmental microbiology and 20-year plus veteran of U.S. industry, 17 June 2004.

As was the case during trial CWC inspections, the U.S. government will be responsible for arranging and bearing the costs of the trials, including transporting, housing, and feeding the inspection team. The industry group concluded that the host facility, even if it were to volunteer, should not be allowed to provide these necessities, in order to avoid the perception that it is trying to influence the inspectors through "wining and dining" them. The host site would not be allowed to give any sort of gift or incentive to any member of the inspection team, nor would it be allowed to host parties. At the conclusion of the inspection, the sponsoring government agency(ies) might organize a farewell dinner.

All participants—including inspectors, government escorts, and other observers—will be required to sign a confidentiality agreement with the host site to provide assurance that any sensitive data or proprietary information will not be disclosed.[15] The industry group specified that this confidentiality agreement must be acceptable to both the inspectors and the host site, not to mention the company's legal council. The host facility would draft this document. Objections to the language of this agreement could be raised and negotiated with the host site, but the document would carry the same text for all participants.

The facility's standard parking regulations should govern the entry of any inspection related vehicles. At most companies, visitors must park in a specially designated lot, and any on-site transportation takes place in host vehicles. Of course, all members of the inspection delegation will be escorted at all times while on site. Throughout their stay, the entire inspection delegation must agree to abide by the facility's safety and security standards. Prior to the inspection, team members must go through a refresher course, either written or via video, on biosafety procedures.

The host site and the government escorts should have the right to inspect and pre-screen any items that members of the inspection team bring into the facility. Either the government escorts or the host could deny access to any piece of equipment deemed irrelevant or inappropriate to the inspection process. The host site will be informed in advance of all equipment that the inspectors plan to bring. The parameters of the inspection do not call for the inspectors to bring any sophisticated equipment with them, only notebooks, pens, and laptop computers. The inspectors could request to bring their own personal protective equipment, but tape recorders, personal digital assistants, mobile phones, or any type of wireless transmission devices should not be allowed under any circumstance. Because many computers are now equipped for wireless networking, host officials may refuse to let the inspection delegation bring their own computers on site. In that case, the host company will provide the inspectors with computers for their use in the designated workroom on site. The inspectors will have use of the workroom for their meetings and drafting of their report.

[15] Note that any infractions of the BWC would be exempt from the confidentiality agreement and could be reported as such. Because the trial inspections would take place at legitimate U.S. biopharmaceutical facilities, no one is expecting any violations of the BWC to come to light.

Though Polaroid cameras have played a prominent role in other types of arms control inspections, the industry group consensus was that a biopharmaceutical firm would be very unlikely to allow an inspection team to bring a camera into its facility, and, therefore, cameras should not be part of the list of potential equipment. If the host site permits the use of cameras or provides a camera to the inspectors, the picture must be printed immediately, either as an instant Polaroid print or through a digital camera printer. Both the inspection team and the host site would retain a copy of the photo to guard against digital manipulation of the image.[16] All electronic gear would be restricted solely to the inspector workroom, but with the host's permission, inspectors may take notebooks and pens into certain areas. The general rule will be that the inspectors must comply with the NIH *Guidelines for Research Involving Recombinant DNA Molecules*, which restrict foreign objects, including computers, pens, and paper, in biosecure areas of the plant.[17]

When CWC trial inspections were underway, the government issued very upbeat press releases prior to trials to stem any potential negative media publicity or misrepresentations that could emerge from an inspection related to weapons. This approach worked well for the chemical facilities involved.[18] Concerned about negative publicity or protests by local citizens who may misunderstand the purpose of the trial inspection, some of the industry experts were cautious about requiring the issuance of a press release. "That is why you have to take control of the situation," countered one expert. "The best offense is a good defense."[19] Therefore, the industry group decided that the host company can choose to keep the trial inspection quiet or issue a pre-inspection press release. If the host site wanted the latter, a press release would be jointly issued with the U.S. government on government letterhead, providing general information on the process while applauding the facility's willingness to volunteer. The industry group suggested that this press release be "as bland as possible."[20]

The media will not be allowed on site during the trial inspection but could attend briefings given to select audiences after the trial to share lessons learned from the experience. The post-inspection briefing process is discussed in more detail in Chapter 7.

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[16] This contrasts with inspections under the CWC, where inspectors are allowed to take photographs using an instant Polaroid camera. Polaroids were chosen specifically because their images cannot be digitally manipulated. The inspection team and the host facility each get a copy of whatever photos are taken, and the inspectors are allowed to take their photos off site as part of the inspection record.

[17] National Institutes of Health, *Guidelines for Research Involving Recombinant DNA Molecules*, Appendix G (April 2002): 68-80.

[18] Prior to the trial at one U.S. chemical plant, the host company "absolutely insisted that the government prepare press releases that are as flowery and complimentary as they can possibly be with all sorts of disclaimers that nothing torrid is going on because the media is quite ready to crucify anybody for the sake of a few headlines." Dr. William D. Carpenter, 8 March 2004. Dr. Carpenter has a Ph.D. in plant physiology and spent his 34-year career at Monsanto, where he retired in 1992 as vice president and general manager for agricultural technology. From 1978 to 1994 Dr. Carpenter represented the Chemical Manufacturers of America in the Chemical Weapons Convention negotiations.

[19] Dr. Robert Goldberg, Ph.D. in medical microbiology with over 30 years experience in research and industry, 17 June 2004.

[20] Dr. George Pierce, professor of applied and environmental microbiology and 20-year plus veteran of U.S. industry, 17 June 2004.

As "the company is going to want to publicize they have a clean bill of health," the facility could issue its own press releases after the inspection.[21] For all press releases and media reports, the names of the participants would remain anonymous, referring simply to Inspector One, the Ombudsman, Escort Two.

[21] Dr. Kay Noel, 8 March 2004. Dr. Noel has a Ph.D. in biophysics and over 20 years of U.S. industry experience. She currently works as a consultant, evaluating new technologies and business opportunities for biotechnology and healthcare companies.

Chapter 5
Pre-Trial Inspection Activities

Prior to the on-site inspection, the industry experts charted two separate pre-trial activities to ensure that host facilities will understand what is going to transpire. The first is a familiarization tabletop exercise, which will provide potential host facilities with an overview of the trial inspection process and allow them to have input to help shape the trial. The second is a pre-inspection preparation exercise to ready the inspection team and tailor it to the facility to be inspected. Both of these activities, described in detail in this chapter, are called "tabletop" exercises because they simulate certain activities. The participants learn by reviewing and analyzing information and talking their way through issues. The second tabletop exercise will kick off the actual trial inspection with the inspectors' examination of open-source information about the facility hosting the trial.

Familiarization Tabletop Exercise

To generate a greater level of awareness, involvement, and cooperation with trial inspections, the industry experts suggested holding a tabletop exercise to walk the top executives of several biopharmaceutical companies through the entire trial process. Industry executives would be invited to this tabletop exercise "because they can commit resources that ultimately we'll need for trials. If you get the right CEO, the people will be there."[1] During this daylong affair, the views of prospective trial hosts would be solicited. Afterwards, discussions would continue with companies interested in hosting a trial inspection. Before their departure, trial organizers would reach preliminary agreement with trial host companies on the aspects of the trial process that meet their needs and expectations. Because the industry brainstormers kept industry's interests in mind throughout the crafting of their inspection hypothesis and trial plans, they anticipate tweaking rather than fundamentally altering the proposed inspection plans. Should host sites raise unforeseen concerns, however, trial organizers will work with them to address those matters, hopefully without compromising the integrity of the trial inspection process.

During the first part of this tabletop exercise, attending companies would be given an overview of the biological weapons proliferation problem, the Biological and Toxin Weapons Convention (BWC), efforts to strengthen it, and past U.S. and international BWC trial experiences. Then the trial organizers would lay out in considerable detail the inspection hypothesis, the trial inspection plan and objectives, and the process for selecting trial participants, among other details. The industry experts recognize that participating in a trial would be a burden for any company and thus fashioned their trial plan to help host companies overcome any qualms they might have about volunteering. To begin with, the trial will be conducted under a confidentiality agreement drafted by the host company, outside participants will be kept to a minimum, and all members of the inspection delegation will have to undergo a biosafety refresher course. Moreover, the inspectors have no purpose other than to test the feasibility of monitoring the BWC's

[1] Dr. George Pierce, 9 March 2004. With a Ph.D. in microbiology, Dr. Pierce has over 20 years of experience in the U.S. pharmaceutical industry and is currently a professor of applied and environmental microbiology at Georgia State University.

prohibitions. The U.S. government will cover all costs for the transport, food, and lodging for inspectors and escorts. Inspectors will bring a minimal amount of equipment, and the host site can refuse any item that does not meet with their approval. An independent trial ombudsman will be present to ensure that any concerns the host company has about the conduct of the trial are aired and resolved promptly and professionally. The host site will have control of any pre-trial press release about the trial and will be granted considerable input into the final report. The post-trial evaluation and reporting activity are discussed in Chapter 7.

The group of industry experts agreed that trial organizers should make companies aware of the full dimensions of the inspection hypothesis and seek industry input on logistical matters. For instance, trial organizers should discuss the interview protocol with host officials, illustrating the types of questions that could be asked so host sites achieve a level of comfort with the process. Industry officials may be somewhat surprised that the hypothesis calls for conducting off-site interviews with contractors and other external entities that have relationships with the company. Trial organizers will also discuss the parameters of the document review with potential host companies, providing a list of the type(s) of documents the inspectors will want to review. Of course, trial organizers will introduce host companies to the protocols for sampling and sample shipment. Industry experts do not expect any company to have reservations about providing a final product sample because it would be the same product commercially available.

To ensure that companies have confidence in the actions that inspectors will take, trial organizers will engage any company that agrees to host a trial in a more detailed discussion about the protocols for on-site inspection activities. For example, the framework for two sampling protocols can be found in Chapter 6, Boxes 10 and 11, but some of the technical specifics cannot be settled until the product to be sampled is known. Among the final product sampling and analysis issues that could be discussed with the site include:

- the exact type of test(s) that will be conducted to confirm identity;
- the certified laboratory that will conduct the tests;
- storage locations for the host site and lockbox samples;
- the appropriate temperature and humidity level for sample storage and testing;
- how the tests will be validated;
- the timeframe within which the test(s) will be conducted, as the sample could be time-dependent; and,
- who will have access to the analytical results.

Some participants suggested that for the trial inspection the Food and Drug Administration (FDA) should be asked to perform the sample identity tests, based on its authority to conduct such tests and perform methods validation as part of the drug

approval process.[2] However, trial organizers and the host facility may agree on an independent, nongovernmental, certified laboratory for this testing. As with other aspects of the trial, the U.S. government will pay for the sample test(s).

Also, potential hosts should be consulted on the anticipated timeframe of the trial. The intent is to conclude the on-site activities within five days, but the trial organizers should explain up front why additional time may be needed. As one expert said, "it's going to always take longer than expected because it is a learning process. Better to be candid and tell the host site officials, 'hey, guys, this might be up to two weeks. This is a learning exercise.'"[3] As trial organizers gain experience, they should be more adept at estimating how long a trial should last for facilities of a certain size and complexity. Even if the trial organizers cannot guarantee the first host sites a five-day limit, they should specify an end date. The industry group also agreed that host facilities might prefer having a larger group of inspectors to ensure the required tasks can be accomplished within five days or less.

With regard to the inspection delegation, the screening process is designed to give host facilities a high degree of confidence that only very qualified and impartial individuals will be participating in the trials. Candidate inspectors, escorts, the ombudsman, and the chemical industry observer will be thoroughly screened. To offer host facilities even more confidence, trial organizers will send the screening dossiers—absent the social security numbers—of the best candidates to the host facility for vetting. Host sites can veto any inspector, escort, or other member of the inspection delegation.

Once the host site sees the dossiers of candidate inspectors, they will appreciate that the inspection process and the qualifications of the inspectors would enable them to readily grasp significant detail about a facility's operations—be it a certain step, process, ingredient, temperature, or other "trick." In short, a facility's trade secrets could be vulnerable to discovery during the trial. One industry expert stated, "for the facility to think that you're going to send a team that is not going to be able to recognize the Holy Grail is very naïve. I don't know how else you get around it. You're going to have to be up front."[4] Host companies should appreciate that to help protect trade secrets all trial participants will be signing a confidentiality agreement that the host facility provides. Furthermore, host companies should recognize a trial as an opportunity to test their internal procedures for safeguarding sensitive information and subsequently develop better procedures for doing so.

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[2] Dr. Robert Goldberg, 8 March 2004. Dr. Goldberg, Ph.D. in medical microbiology, has over 30 years of research and administrative experience in U.S. industry and at the National Cancer Institute; Dr. Kay Noel, 8 March 2004. Dr. Noel has a Ph.D. in biophysics and over 20 years of U.S. industry experience. She currently works as a consultant, evaluating new technologies and business opportunities for biotechnology and healthcare companies.

[3] Dr. Jennie Hunter-Cevera, 8 March 2004. Dr. Hunter-Cevera is president of the University of Maryland Biotechnology Institute with over 20 years of research and managerial experience in U.S. industry and research institutions and a Ph.D. in microbiology.

[4] Ibid.

Finally, the industry experts decided that host sites should be offered the opportunity to place a company observer on the inspection team to give the company a deeper understanding of the inspection process. This person would observe *all* phases of the inspection, from the pre-inspection data review to the final report drafting, including inspectors' meetings and discussions. This observer would not have any actual inspection duties. Further, this observer would not act as an escort or liaison between the host facility and inspectors. While serving in this capacity, the company observer would agree to refrain from discussing any aspect of the inspection with other personnel from the host company. This observer would file a separate report during the evaluation following the trial, as described in Chapter 7. Of course, in an actual inspection, the host site would not be allowed to infiltrate the inspection team. The industry experts view the host company observer not just as a courtesy to the host facility, but as another way to more directly inform and involve industry about efforts to develop a viable inspection process.

Pre-Inspection Data Review and Inspection Team Preparation Exercise

The official first step of a trial inspection will be a tabletop exercise where the inspection team will review a considerable amount of data to become as familiar as possible with the facility they will inspect. The industry experts crafted a major pre-inspection open-source information grab and analysis process for the inspectors for several reasons. The hypothesis calls for the facilities to make very modest data declarations, as Box 4 indicates. For commercial companies, a great deal of information useful to the inspectors is there for the taking, and industry experts believe BWC inspectors would be foolhardy to forsake any chance to prepare themselves better for the upcoming inspection. The inspectors will need to make the most of open-source data if they are to be efficient and effective with their time on site. Capitalizing on the availability of open-source data also safeguards the inspection team from being misled by host officials. So, the inspectors will crunch available data to shape their expectations about the facility, identify areas of focus for the inspection to come, and decide what additional expertise, if any, should augment the core inspection team.

Box 4: Content of Facility Data Declarations Prior To Inspection

Manufacturing Facility	Development Facility
• Type of product(s) being produced • Quantity of product(s) being produced	• Type of research and development being conducted • Complete description of the type and quantity of select list agents, simulants, closely related organisms and/or toxins on site, including any genetic modifications or potential dual-use agents

Two activities need to occur to set the stage for this tabletop exercise. First, as described in the previous chapter, the trial organizers need to screen candidate inspectors and vet their names with the host facility. Second, the data to be analyzed needs to be gathered.

The industry experts suggested that the task of collecting and organizing this open-source information should be delegated to administrative support staff of a U.S. government agency helping to organize the trial. Another option would be for the U.S. government to outsource this task to a data collection company, which could compile this information efficiently within a reasonable timeframe.

Whether in a real inspection or a trial, the facility to be inspected would not be required to provide data beyond the bare-bones data declaration specified above, and host facilities may redact confidential data from this initial declaration. Facilities may, however, volunteer additional information. "The company or facility that wants a clean bill of health is going to do everything they can to comply with this and do a credible job. Those people that have something to hide, basically, we're asking for them to commit suicide. If they hold back on information we will find it later, because all of this is public information," said one industry veteran.[5] Therefore, legitimate companies would consider it in their own best interests to cooperate with the inspectors as much as possible, including by providing more than just the data required for declarations, short of sharing confidential business information.

Given the abundance of publicly available information, the industry experts listed numerous open sources that should be tapped for useful data. Many of these sources are now available electronically, which will make data collection easier. Government records that are not available on-line may be requested through the Freedom of Information Act. The industry experts' recommended data sources and types of information are listed in Table 5. The industry experts consider this information to be critical to helping the inspectors understand what they should expect and might encounter on site. For example, in looking at a facility's links with government and its intellectual property and patent portfolios, one industry expert said: "A facility is not going to engage in biological weapons unless they've got state support. Do they have a contract to supply things for the state? Looking at patent/intellectual property portfolios, all of a sudden you find a couple of people on a facility's roster who have patents in aerosol technology. That doesn't make sense at a baby food factory."[6] This type of investigation and discussion would typify the pre-inspection data analysis session at trials or actual inspections. The table below also highlights with underlined type the information deemed to be useful, but non-critical to a pre-inspection data analysis.

Obviously, the inspectors will have a mountain of data to review. To organize this information so that the facility can be characterized, the industry experts agreed that the documents should be separated into five categories: 1) adverse events/action; 2) personnel; 3) corporate and facility history; 4) locations; and, 5) current activities. Insights into a company's history of adverse events/actions can be found in government records. The documents relevant for understanding a facility's history are a company's product profile, clinical trials, research activities, partnering/teaming/licensing arrangements, prior association with bioweapons defense work, and government records

[5] Dr. George Pierce, professor of applied and environmental microbiology and 20-year plus veteran of U.S. industry, 8 March 2004.
[6] Ibid.

of certifications and activities. Inspectors can review the pedigrees of a company's key executives, administrators, and scientists through their scientific papers, presentations, patents, and in-house publications, clinical trials, financial/business news, annual reports, government documents, awards, and honors. The inspectors can also consider the international connections by looking at their scientific and business collaborators. A view of facility locations can be gained through Environmental Protection Agency databases, patents, and scientific papers. Finally, a site's current activities can be traced through its research areas/trends, clinical trials, and products.

Table 5: Data Collection and Analysis Architecture

Information Sources	Type of Information To Be Collected	Analytical Categories
Publicly Available From Company	• Company's annual reports and financial reports • Company-issued press releases and public statements	• Personnel • History • Locations • Current activities
Electronic scientific databases	• Staff publications, including their citations indexes and *curricula vitae* • Staff presentations	• Personnel
Electronic databases on federal government grants, contracts	• *Curricula vitae* of company staff • Manufacturing/research contracts with the federal government[a] • Securities Exchange Commission reports[b]	• Personnel • History
Lexis/Nexis legal database	• Fines • Prosecutions	• Adverse events • History
U.S. Patent and Trademark Office and Derwent patent databases	• U.S. patents • International patents	• Personnel • Current activities • History • Locations
Business information databases	• Major capital projects (intent, size, location) • Products, pre-clinical, clinical trial • Other business reports on the facility, company	• History • Locations • Current activities
Food and Drug Administration	• 483s[c] • Letters of warning[d] • Recalls[e] • Section 301 seizures[f] • Consent decrees (permanent injunctions)[g]	• Adverse events • History

Table 5: Data Collection and Analysis Architecture (continued)

Information Sources	Type of Information To Be Collected	Analytical Categories
Environmental Protection Agency	• Superfund Amendments and Reauthorization Act, Title 3, Section 312 Annual waste reporting[h] • Toxic Release Inventory • Pollution Prevention Act of 1990 • Resource Conservation and Recovery Act[i] • Superfund sites	• Locations • Adverse events • History
Centers for Disease Control and Prevention	• Facility biosafety certifications • Disease outbreak reports in the vicinity of the facility to be inspected	• Locations • Adverse events • Current activities • History
Local, regional newspapers Activist/advocacy groups	• News stories pertaining to a disease outbreak near the facility • Other stories involving the facility but not pertaining to disease outbreaks	• Adverse events • History • Current activities • Locations • Personnel

[a] Initial notice of contract awards will provide limited data. More information could be obtained through Freedom of Information Act requests.
[b] Companies are required to file annual reports that give an accounting of their business and financial status. These 10-K Reports are available on the Securities and Exchange Commission website, www.sec.gov.
[c] FDA-483 reports detail "objectionable practices or deviations" from FDA regulations, as revealed through FDA inspections. Approximately 7,500 are reported annually, and are available online at www.fda.gov.
[d] The FDA issues approximately 1,300 letters of warning each year.
[e] FDA recalls are divided into three categories. Class 1 recalls involve faulty products that could result in serious injury or death. Class 2 violations could result in moderate or temporary illness, and Class 3 recalls are unlikely to cause illness. FDA and company press releases describing individual products that have been recalled are searchable online at www.fda.gov. The FDA recalls approximately 4,500 products per year, mostly related to food.
[f] Section 301 of the Federal Food, Drug and Cosmetic Act lists prohibited acts related to food, drugs, devices, and cosmetics, while Sections 303 and 304 detail procedures for imposing penalties and seizures for such violations. Federal Food, Drug and Cosmetic Act, Chapter 3, Prohibited Acts and Penalties, www.fda.gov.
[g] The FDA issues an average of 12 to 15 consent decrees per year.
[h] The Superfund Amendments and Reauthorization Act governs the Environmental Protection Agency's administration of the Superfund program to clean up the nation's hazardous waste sites. See www.epa.gov/superfund.
[i] The Environmental Protection Agency maintains a database of information on facility activities under the Resource Conservation and Recovery Act and the handling of hazardous waste. See www.epa.gov/rcraonline.

After the open-source data is collected and the core inspectors are selected, a two-day tabletop exercise can be scheduled. The ombudsman and official trial observers would sit in on the tabletop exercise, but the core inspectors themselves would be analyzing the data thoroughly and making their preliminary decisions about the upcoming inspection.

During this tabletop, the inspection team would begin developing working relationships with each other and get comfortable in their roles as inspectors. Relevant U.S. government officials would be invited to observe the tabletop activity, but their presence would not be mandatory. One group member noted, "it might be helpful for them to see that this isn't a piece of cake either to gather or to analyze" all of this data.[7] U.S. officials would certainly be encouraged to attend the wrap-up/evaluation session to be briefed on what transpired and ask questions of the core inspectors.

Even from the relatively concise data declarations that facilities are required to provide, professionals seasoned in scientific and industry affairs will have expectations as to what would be considered normal scientific, technical, and business practice for the type of activities that a facility has declared. The five-pronged data analysis will also bring into focus any areas where the facility might be inconsistent with standard practice. In the words of one industry expert, "this is our due diligence prior to the inspection, so we'll shape and frame the team and what to look for based on the open record."[8] For a manufacturing facility, the inspection team will probably shape expectations regarding three key aspects of the facility: the level of biosafety containment, the waste treatment system, and the operational set-up of the facility. With regard to a development site, the inspectors will hone their expectations for equipment, scale-up process, and health and safety requirements that would be appropriate for the type of facility they will be inspecting. They should also contemplate what type of animal facility, if any, to expect at the site.

Once expectations and possible deviations from standard practice are framed, the inspection team can identify and make a tailored list of priority areas for further investigation. Thus, in the latter stages of the tabletop, the team will define its focus areas for the initial site tour and the document review. The team will also sketch preliminary interview questions and cross-checking tactics.

Based on what is learned through this open-source data review, the team leader can customize the inspection team with additional specialists. When the team leader knows that a facility is working with a certain organism, the prudent thing to do is to equip the team with its own ace— someone who has worked with that very organism. Otherwise, the inspectors risk being caught unaware of standard practice or deviations from it that should prompt questions, as was the case in a 2000 trial inspection of the Public Health Research Institute in New York City.[9] Said one participant, "we want to send the best

[7] Dr. Kay Noel, Ph.D. in biophysics and a consultant for biotechnology and healthcare companies with over 20 years of industry experience, 8 March 2004.

[8] Dr. Jennie Hunter-Cevera, Ph.D. in microbiology and president of the University of Maryland Biotechnology Institute, 8 March 2004.

[9] The Public Health Research Institute has 22 research laboratories working in a variety of areas, but the trial centered on a biosafety level 3 laboratory that characterizes strains of tuberculosis. The two inspectors were former military officers who both had extensive bioweapons inspection experience, but neither had ever worked with tuberculosis or *Bacillus subtilis*. For the purposes of the trial, the host facility's trial organizers planted several clues for the inspectors that, had they been seen and understood, would have given rise to suspicions of bioweapons-related work. The inspectors either did not recognize these clues or did not understand the significance of the ones they observed. For more, see *House of Cards: The Pivotal*

team, and the best thing to do is have a team that's prepared so they don't go totally cold to the site."[10] Based on this thorough information analysis, the team leader could add as many as five individuals to a manufacturing inspection and seven additional specialists for a development facility inspection, as indicated in Chapter 4, Table 4. Of course, the new team members would be screened by the trial organizers and vetted by the host site. Prior to the inspection, they would be asked to review all pertinent materials about the facility and provide input into the customized inspection strategy created at the tabletop exercise. With an in-depth profile of the facility and an inspection strategy in hand, the team leader would consult with inspection team members and give the core and auxiliary inspectors their initial assignments for the site tour, document review, and interviews to be conducted on site.

Just prior to departing for the inspection, the industry experts' hypothesis calls for the inspection team to have the benefit of satellite imagery of the facility to be inspected. The purpose of consulting historic and recent satellite images is to see how the facility has changed over time and, importantly, to guard against a flurry of construction or unusual—perhaps cover-up—activity in the days after a facility has received notice of an inbound inspection. Professional image analysts would need to assist the inspectors to understand what information can be gleaned from this data source. At a minimum, the inspectors will have a very clear idea of a facility's layout, which will come in handy if host officials consistently steer them away from a certain building or area. For the purposes of trials, the industry experts prefer to have this activity included as a final pre-inspection briefing for the inspection team, but understand that the costs of doing so may be prohibitive.

Importance of a Technically Sound BWC Monitoring Protocol, report no. 37 (Washington, DC: Henry L. Stimson Center, May 2001): 46-47.

[10] Dr. George Pierce, professor of applied and environmental microbiology and 20-year plus veteran of U.S. industry, 8 March 2004.

Chapter 6
Trial Inspection Activities On Site

Due to the measures that the industry already takes to comply with existing U.S. regulations, the host site should naturally be prepared for a Biological and Toxin Weapons Convention (BWC) trial inspection, particularly a manufacturing facility. "If they're doing their job," said one industry expert, "there shouldn't be any preparation, because they've been through Food and Drug Administration inspections and those mock inspections to prepare for the FDA all the time."[1] Having approved the inspection delegation, the facility should have an appropriate amount of biosafety protective gear (e.g., sanitary gowns, booties) available. The plant manager should also explain to the staff what the expectations of the staff are and that the inspectors are there for no other purpose than to test the ability to monitor the BWC's prohibitions against developing, manufacturing, and stockpiling germ weapons.[2] The facility management would be well advised to have a communication strategy, both internally to share information with the staff and externally to deal with any media or public inquiries. The host company should also make sure that the appropriate staff members are on site, available for interviews with the inspectors.[3]

In devising a trial inspection plan for development and manufacturing activities, the industry experts assumed that it would be best to craft a step-by-step approach to test whether BWC compliance can be monitored at industry facilities. The industry experts assumed that it will be more challenging to evaluate BWC compliance at development facilities than at manufacturing plants. Therefore, the trial inspection scheme initially calls for separate trials of manufacturing and development activities, although the same overall inspection strategy and tactics would be applied at both types of sites. The industry experts recognized that trials had to be tolerable to industry. Therefore, trial inspectors will not initially push either the inspection strategy or tactics to the limits, as this chapter describes. Rather, at the outset they will give all of inspection techniques reasonable tests. Box 5 diagrams the general flow of on-site monitoring activities, as well as of this chapter.

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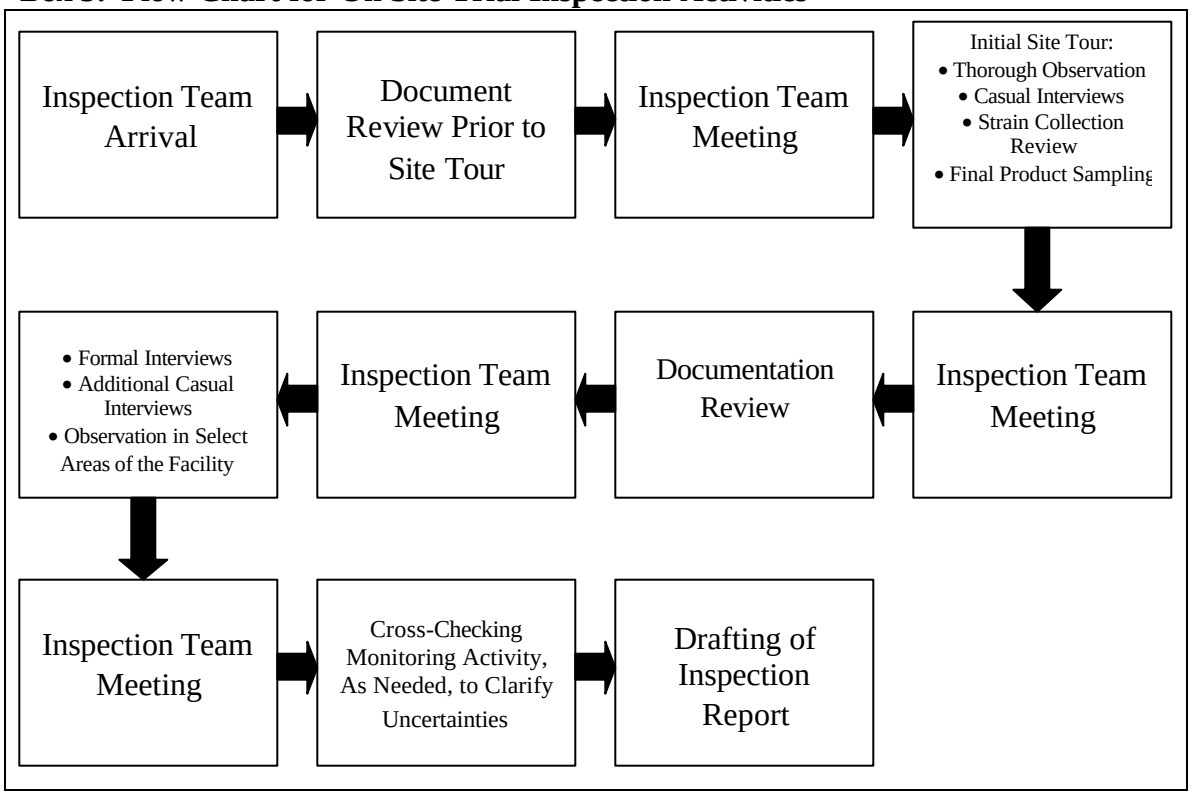
[1] Dr. Jennie Hunter-Cevera, 8 March 2004. Dr. Hunter-Cevera is president of the University of Maryland Biotechnology Institute with over 20 years of research and managerial experience in U.S. industry and research institutions and a Ph.D. in microbiology.

[2] The inspectors are not there representing the Food and Drug Administration or any other U.S. regulatory agency. The final inspection report would record *only* violations pertinent to BWC compliance. In private consultation with the host officials after the inspection, the inspectors would raise any other U.S. regulatory violations they may have noticed so that the company could take the appropriate steps to bring itself back into regulatory compliance. The U.S. government escorts will not attend this private discussion.

[3] Were multiple key staff members unavailable for interviews in a real inspection, the inspectors would consider it an ominous sign.

Box 5: Flow Chart for On-Site Trial Inspection Activities



As companies and inspectors gain confidence in the safeguards built into the process and in the utility of the trials, the inspectors will gradually begin to press the strategy and tactics harder. Trials will conclude with the writing of the draft inspection report, which is described in the next chapter. During description of the trial inspection process in this chapter, many passages illuminate how the inspectors would perform their jobs in a real BWC inspection, describing what would rouse the inspectors' concern and how they would use various inspection techniques to clarify matters.

The Initial Site Tour

When the inspection team arrives at the facility, they will have well-formed expectations about the site and pre-identified specific areas of focus based on prior analysis of open source materials. The initial tour will be extensive and interactive in the sense that inspectors will ask questions along the way. From the moment they step on the grounds, inspectors will be trying to identify inconsistencies with normal scientific and industrial practice, which will be the areas where they will probe deeper during the subsequent interview and document review phases.[4] The inspection crew would also obtain a sense of the normal work atmosphere at the site during the tour. Throughout their stay, the

[4] In a previous meeting, the industry group critiqued the BWC Ad Hoc Group's draft inspection protocol, concluding that the proposed two-hour site tour would be akin to "a high school tour," not a genuine compliance monitoring effort. *House of Cards: The Pivotal Importance of a Technically Sound BWC Monitoring Protocol*, Report no. 37 (Washington, DC: Henry L. Stimson Center May 2001): 92. For details on the BWC Ad Hoc Group's draft protocol, see *Procedural Report of the Ad Hoc Group of the States Parties*, BWC/Ad Hoc Group/51 (Geneva: 6 April 2000).

inspectors will assess the host officials' willingness to cooperate with reasonable requests. During their evaluations after different phases of on-site activity, the inspectors will note any areas where the hosts refused to provide information or access and why access was denied, if an explanation is given.

Certain agreed rules will guide the behavior of inspectors and host officials alike during the initial site tour. As inspectors begin to move through the facility, they will wear the appropriate biosafety and other protective gear. For the host facility, the inspection hypothesis allows for very limited shrouding of certain equipment, items, or material that the site views as proprietary and non-relevant to the purposes of the inspection.[5] This policy is in line with industry practice. Said one industry expert, "many companies claim certain aspects of their process are proprietary. That's common, and they will shroud."[6] For trials at manufacturing facilities, the host site can shroud manufacturing lines other than the one making the declared product being inspected. However, at development and manufacturing facilities, shrouding should be kept to the *absolute minimum*. Otherwise, inspectors may not be able to assess compliance. Should inspectors ask questions, facility operators should be prepared to explain why an item is shrouded. Said one industry expert, "we want to be able to actually see the full facility."[7] Of course, the inspectors will be bound by a confidential disclosure agreement, which would obligate them not to disclose any sensitive information they may come across during the inspection.

During the trial, the inspectors will have the right to ask to take pictures inside the facility, but the host has the right to refuse photographs altogether or a particular request for a photograph. Should host officials agree that one or more photographs can be taken, they have the option of providing a Polaroid-style instant camera or a digital camera that allows instant printouts. Once printed, the picture would be removed from the digital camera to prevent manipulation of the image. Should the host not want one or all photograph(s) to be part of the final record, the photograph(s) will be destroyed at the end of the inspection. The host company may choose to videotape the trial inspection and use this as a training tool for future inspections.[8]

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[5] Shrouding is a generic term that covers steps taken to conceal a certain item or capability that facility operators deem sensitive and unrelated to treaty compliance. For example, a tarp might be thrown over a proprietary piece of equipment or a small portion of that equipment might be concealed (e.g., the instrument dials). Or, in the storeroom, plant operators may choose to mask the identity of a key ingredient.

[6] Dr. George Pierce, 8 March 2004. With a Ph.D. in microbiology, Dr. Pierce has over 20 years of experience in the U.S. pharmaceutical industry and is currently a professor of applied and environmental microbiology at Georgia State University.

[7] Dr. Claude Nash, 17 June 2004. Dr. Nash, Ph.D. in microbial genetics, is vice president of research and development for the University of Maryland Biotechnology Institute, founded his own biotechnology company, and has over 30 years experience in industry.

[8] Should the host facility opt to video the exercise, the inspection team would have the right to review the tape to ensure that video represents their actions accurately, adding an addendum if necessary. Obviously, a videotape of the trial would be a useful educational tool for the inspectors as well. Trial organizers will request the ability to videotape for that purpose, but the industry brainstormers expect that host facilities would be very reluctant to grant permission to record the exercise.

In addition to visual observation and verbal exchanges with facility personnel during the initial tour, the inspectors will take certain steps to examine a facility's strain collection(s) more closely. At a manufacturing plant, the inspectors will also take a final product sample. Before these activities begin, however, the inspectors will review additional documentation that will allow them to validate their initial inspection strategy and tactics.

Revising the Focal Points for the Initial Site Tour

The inspection hypothesis calls for the inspectors to hit the ground running, beginning the site tour as soon as possible after entering the premises.[9] However, the industry experts explained that the inspectors would need certain documents in hand to make the site tour a truly informative endeavor. Box 6 lists the set of documents that the host facility would be expected to provide as the inspection team arrives. Ideally, the inspectors would have these documents before arrival, but realistically, companies would be very reluctant to provide them in advance.[10] Therefore, time has to be set aside for the inspection team to digest this material prior to the tour. The industry experts estimate that four hours would suffice.

Box 6: Documents to Facilitate the Initial Site Tour

- Site map(s)
- Floor layout
- Architectural diagrams
- As-built engineering diagram
- Piping and instrumentation diagram
- Equipment list
- Organism strain list and use log
- Utility profile
- Process flow diagram(s).

The inspectors are to consider these documents confidential and not to be removed from the site, with the exception of a schematic of the process flow diagram. This document can include sensitive proprietary data, and, ideally, the host facility will provide inspectors the actual process flow diagrams to review. If they decline to do so, the facility will provide the inspectors with a schematic, specific to the processes being scaled up or the product being inspected. This schematic will identify basic steps but

[9] The industry experts stipulated that the inspectors get off the mark smartly to minimize the host's ability to stall or delay the tour through an extensive greeting or orientation session. Prior to arrival on site, all team members will have taken a biosafety refresher course, so a lengthy safety briefing should not be required.

[10] The trial organizers can encourage host facilities to provide these documents beforehand, said one industry expert. "[I]t doesn't hurt to state that in putting together this trial inspection, we've already made a real compromise here. We would rather have this information up front, but to try to make it as easy as possible for compliance, we'll deal with it on site." Dr. George Pierce, professor of applied and environmental microbiology and 20-year plus veteran of U.S. industry, 8 March 2004.

may obscure with blank boxes steps unique to the process. This schematic would be confidential but could be taken off site as part of the final inspection report.[11]

To illustrate how the inspectors would employ these documents as they walk through the site, the utility profile would show them a facility's energy capacity and flow. Comparing this with the equipment list and what inspectors see as they tour the site, the utility profile provides an initial check "to make sure that they have the right amount of energy to do what they say they're doing. If they have all of these backup generators and excess energy capacity, then questions should be asked."[12] Inspectors must also be tuned into the possibility that a site host might provide them with a bogus piping and instrumentation diagram. Because this document can be easily created on a computer, the inspectors should look for any incongruous walls, doors, piping, vents, or other indicators that the plant layout does not match the diagram. The inspectors need to be on guard because aside from carefully mislabeled strains, which are addressed later in this chapter, a false piping and instrumentation diagram is one of the most challenging deceptions inspectors will need to avoid.

The initial facility tour could last a half a day or longer, depending on the cooperativeness of host officials and the characteristics of the inspected facility. All sites are designed differently, but generally the inspectors should anticipate the need to spend more time touring a development facility than a manufacturing facility. Production plants tend to have "a big room filled with fermentation vessels," as opposed to development sites, which typically include "little rabbit warrens that they build into basic research areas. It takes a long time to discover every room in the building."[13] On the initial tour of a development facility, the team should pay particular attention to quantities of biological materials, the type of facility (e.g., equipment, animal facilities, scale-up process), and health and safety structures. Box 7 shows a more thorough listing of generic walk-through inspection focal points. At a manufacturing plant, the inspectors would be looking particularly closely at the production area, waste-handling facility, laboratories, and organism storage areas.

After reviewing extensive open source information about the facility, as described in Chapter 5, the core inspectors will have begun to put specificity into their inspection tactics by underscoring more customized focal points for the initial site tour and document review. They will also have drafted an initial list of questions to pose to staff personnel during the site tour and in formal interviews. With the benefit of the details contained in the documents listed in Box 6, the inspectors will be able to give their initial inspection tactics a final scrub, sharpening their focal points and questions. The team leader will delegate responsibilities for asking certain questions and examining specific matters of interest to individual team members.

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[11] U.S. manufacturing facilities regularly provide their process flow diagram(s) to FDA inspectors.

[12] Dr. Jennie Hunter-Cevera, Ph.D. in microbiology and president of the University of Maryland Biotechnology Institute, 17 June 2004.

[13] Dr. Dennis M. Gross, 17 June 2004. Dr. Gross, Ph.D. in cell biology, is an adjunct associate professor of biochemistry and molecular pharmacology at Thomas Jefferson University's College of Medicine and College of Graduate Studies in Philadelphia with 25 years of experience with a Fortune 100 U.S. pharmaceutical company.

Box 7: Generic Focal Points for an Initial Site Tour

- Analytical, microbiology laboratories
- Air handling systems
- Utility supply
- Appropriate level:
  - Containment
  - Capacity
  - Biosafety equipment
- Behavior of employees
- Equipment:
  - Set-up
  - Connections (e.g., mobile, fixed)
  - Partitioning
  - Appropriate purification
  - Standard operating procedures/protocols
- Storage area:
  - Labels
  - Quantities
  - Types
- Waste handling:
  - Design
  - Construction
  - Operations
  - Intake/outflow
  - Standard operating procedures/protocols
- Animal facility:
  - Level
  - Numbers
  - Appropriate models
  - Standard operating procedures/protocols
- Scientists' notebooks:
  - Bound, numbered pages, not loose leaf papers

Touring the Facility

The inspectors will embark on the initial site tour looking for inconsistencies with standard business and scientific practices and their other expectations. The one thing that the inspectors really should anticipate, counseled one industry veteran, is some deviation from their expectations. "I have never walked into a plant where I didn't find something [unexpected] along the way."[14] The inspectors will explore as much of the facility as possible, essentially adopting a "go-until-stopped" attitude. According to their

[14] Dr. Kay Noel, 8 March 2004. Dr. Noel has a Ph.D. in biophysics and over 20 years of U.S. industry experience. She currently works as a consultant, evaluating new technologies and business opportunities for biotechnology and healthcare companies.

assignments, team members should casually talk to facility personnel, asking them pre-identified questions in a variety of ways. Some questions will be asked multiple times. Such informal questions could reveal a significant amount about the plant's operations, including whether the technicians are comfortable with their jobs. Said one industry expert, "there's no such thing as a stupid question. There are stupid answers. And you can ask anything you want, and if they give it to you, okay. Always ask."[15] After the tour, inspectors will compare notes. At that time they will also assess the level of cooperation they received throughout the tour.

One not-so-subtle sign that a facility may be trying to sweep something under the rug is undue delay during the tour. As noted, the inspectors are required to wear the appropriate biosafety gear (e.g., booties, laboratory coats) in various areas. The inspectors, having all worked in biosafety environments, will be very familiar with this drill. Therefore, they will recognize if facility hosts put them through over-the-top precautions to stall and consume time. Recalling an experience inspecting a bioweapons facility in another country, one brainstormer said the host officials "would play this game. They had a truck driver type of nurse who made us strip, took an axillary temperature, and then checked us out even further. They did that to waste our time, but they let us in eventually."[16] Another claim that inspectors would recognize as inflated is an attempt to keep them out of certain rooms because they would "contaminate" a product. Because the inspectors will don the same protective gear as those working in such rooms, this should not be an issue.[17]

At practically every turn, inspectors will be faced with facets of the facility to assess. For example, having reviewed the equipment list, the inspectors should ask for clarification about missing, extra, or broken pieces of equipment. One expert said that the analysis of equipment should be quantitative *and* qualitative, such as whether centrifuges are high- or low-speed. "If they see a piece of equipment that they know is not related at all to making that final product, then, qualitatively, they're going to really challenge that. Ask for an explanation as to what the heck *that* is doing there."[18] In short, the team will consider whether the equipment is appropriate for manufacturing the declared product or pursing a certain development activity. When the inspectors assess a development activity, they will examine whether the quantity of lethal or infectious doses of select list agent(s) that the site possesses matches what would be expected for the facility's declared

[15] Dr. George Pierce, professor of applied and environmental microbiology and 20-year plus veteran of U.S. industry, 8 March 2004.

[16] Dr. George Robertson, 18 June 2004. Dr. Robertson, vice president for the science and technology division of PDA, has over 30 years of experience in industry and biodefense and holds a Ph.D. in molecular biology.

[17] Note that access in certain areas of an animal facility may be very limited for legitimate reasons. Inspectors will know this as well and will be able to suggest alternative ways (e.g., remote viewing through a video camera, extensive review of documentation associated with preclinical trials) to investigate the preclinical trials facility.

[18] Dr. Robert Goldberg, 18 June 2004. Dr. Robert Goldberg, Ph.D. in medical microbiology, has over 30 years of research and administrative experience in U.S. industry and at the National Cancer Institute.

activities.[19] The inspectors will also check to see if inventories of other key materials are in line with their expectations.

The inspectors should be instructed to follow any questionable piping or ventilation chambers until the host stops them. Likewise, if the inspectors feel the host is intentionally steering the team away from a particular area, they should directly ask host officials if this is the case. "As they are getting a flavor for the facility, something doesn't seem right. People don't know the SOPs and they're not properly done. If they do this in front of an inspector," said one industry expert, "what are they doing when inspectors aren't there?"[20] Such oddities would certainly raise suspicions of foul play.

As they make their way through the facility, inspectors must be on the alert for such signs. One of many such signs would be a higher level of biosafety containment than is necessary for the stated activities. Said one industry expert:

> Basically, too much containment makes a big world of difference, including cost. If a company has a lot of biosafety level 3 equipment and containment for a biosafety level 2 or less product, that doesn't read right. They're spending buckets of money they don't need to spend. You're always told to adhere to the letter of the law, as far as compliance goes, but not to spend another nickel because, in most cases, that extra nickel doesn't buy a nickel's worth of safety.[21]

The challenge for inspectors will be to figure out whether a company has sound reasons for putting a level 2 operation in a biosafety level 3 facility.[22] Inspectors will no doubt find additional food for thought in the facility's waste handling area and preclinical trials facility, should one be present. Inspectors may not be able to figure everything out on the first pass. Diving into a review of a facility's documentation and conducting

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[19] The terms of art used to describe lethal and infectious doses are LD_{50} and ID_{50}. The U.S. Centers for Disease Control and Prevention defines LD_{50} as "a single dose of a material expected to kill 50 percent of a group of test animals. The LD_{50} dose is usually expressed as milligrams or grams of material per kilogram of animal body weight (mg/kg or g/kg). The material may be administered by mouth or applied to the skin." See www.cdc.gov. Similarly, the infectious dose 50 (ID_{50}) is the dose that would infect 50 percent of a target population.

[20] Dr. George Pierce, professor of applied and environmental microbiology and 20-year plus veteran of U.S. industry, 8 March 2004.

[21] Ibid.

[22] Many companies intentionally overbuild to allow room for future growth, so to explore such circumstances inspectors should pay close attention to the laboratory procedures and biosafety protocols to distinguish why the excess capacity exists. If a site is equipped for biosafety level 3, but claims to be working only with organisms requiring level 2 containment, inspectors should determine whether the facility has been operating and maintaining the biosafety level 3 containment, including changing filters and looking at the high efficiency particulate arresting filter exhaust. Also, associated records and documentation can be scrutinized. "They're going to have maintenance records," asserted one group member, "even if they don't care about anything else, they don't want the biosafety equipment breaking down." Dr. Dennis M. Gross, adjunct associate professor of biochemistry and molecular pharmacology at Thomas Jefferson University's College of Medicine and College of Graduate Studies in Philadelphia and 25-year industry veteran, 18 June 2004.

additional interviews will help inspectors determine the true nature of a facility's activities.

Examining a Facility's Strain Collection(s)

A large industry facility is likely to have more than one location (e.g., freezers, refrigerators, and shelves) where the organisms it works with are stored. The inspectors will have three basic objectives in mind as they check a facility's strain collection(s). Inspectors will endeavor to corroborate that the strain collection(s) are properly stored, with appropriate access conditions, and that appropriate inventory logs are kept. Finally, inspectors will check labels on freezer/refrigerator contents to see if they correlate to listed strains/cultures and batch records. They will perform these chores informed by a detailed list of the strains stored on site, as well as the quantity in stock and the use-log, which will enumerate who has worked with the particular strains. The other documents that inspectors will require to assist their inspection of a site's strain collection(s) are found in Box 8.

Box 8: Documents Required for Inspection of a Facility's Strain Collection(s)

- Strain lists, including where and how strain was acquired or developed;
- Permits for use of strains, specifying species/strain and personnel authorized to use;
- Shipping and receiving records for strains/cultures;
- Listing of personnel cleared to use strains/cultures;
- Standard operating procedures for:
    - Receipt and shipping of strains/cultures,
    - Verifying organism species/strains,
    - Storage and handling of strains/cultures;
- Batch record listings, including species/strain/culture used, number of tubes withdrawn from inventory, date of use, and amount and type of materials generated; and,
- Freezer/refrigerator inventory logs and/or database

The industry experts' proposed protocol for inspecting strain collection(s) can be found in Box 9. Inspectors will take time to confirm that the vials in freezers are clearly labeled and the quantity and type are consistent with their expectations of that facility. The inspectors will accomplish this task with a combination of targeted and random inventory spot checks. The inspectors should also ascertain whether the storage temperatures are consistent with the designated product. During this part of the inspection, the pedigrees of organisms of interest can be established, such as whether the strains/cultures were acquired or developed in-house. Trial organizers will review this protocol with host facilities prior to trial inspections.

Box 9: Protocol for Inspection of Strain Collection(s)

To verify that the company is working with the agent(s) it declares, inspectors will investigate a facility's strain collection(s) using the following procedures:

1. The inspectors will consider whether freezers/refrigerators containing the declared agent(s) are located in area(s) with the appropriate restricted, controlled, and/or locked access.
2. Inspectors will substantiate whether the specified storage conditions for the declared agents(s) are being maintained.
3. Referring to the list(s) of personnel cleared to access/use the strains/cultures, inspectors will determine whether that list corresponds with permits from the Centers for Disease Control and Prevention and/or the U.S. Department of Agriculture.
4. Inspectors will request inventory logs that list the user, strain required, lot, and lot size for each use, taking note of how and where such records are stored. When electronic databases are used, inspectors will study who has access to data entry and editing privileges. Inspectors will confirm that data entry is consistent with inventory logs for the freezer/refrigerator.
5. Inspectors will survey the entire suite of documentation for the strain collection(s), looking for strains/cultures that would be inconsistent with expectations for the facility being inspected, including usual strains/cultures that go beyond the scope of the facility's certifications or work patterns.
6. Inspectors will pull the vials with declared agent(s) from freezer/refrigerator contents, looking at labels to see that if they are consistent with listed strains/cultures and batch records. Inspectors will also perform the same procedure with a small percentage of the remaining inventory, randomly selected, to validate the accuracy of documents against freezer/refrigerator inventories.
7. Inspectors will scrutinize the pulled strains/cultures to see if they correspond to permits for possession and use. They will also survey the inventory to see if the number of tubes of strains/cultures is consistent with batch records.
8. Inspectors will study the overall condition of freezer/refrigerator inventories, looking for unusual labeling, organization, frost patterns, or other signs inconsistent with normal strain collection maintenance and use.

This facet of the inspection could be cumbersome in a development facility that does not have a central collection repository. Even in facilities with central repositories, many scientists maintain their own databases "because they don't want to spend the time using a centralized collection. After a while they stop using it [the central repository] because it is an onerous task. They can just do it themselves." As one industry expert explained, the inspectors will then have to cope with many separate sets of records, "data islands all over the company."[23] However, while these multiple strain collections and records may

[23] Ibid., 17 June 2004.

complicate the inspectors efforts, "bad paperwork is not necessarily, or is probably not, an intent to deceive. It's just the organization of the lab."[24]

Alternatively, should inspectors pick up on something possibly amiss when examining a facility's strain collection, it could be an indication that the facility is trying to conceal the real nature of its activities. Site operators could intentionally misname organisms—referring to a select agent such as anthrax as something more benign—on labels and in laboratory notebooks and other records. A diligent inspector could detect the deception through the level of containment and type of equipment being used as well as the type of media, temperatures, and growing conditions that are employed. However, this would be much more problematic if the organism in question is cleverly mislabeled as a closely related but non-threatening substitute, particularly if both use the same type of media. In such a case, sampling may be the only sure way of confirming the contents of a site's strain collection.

On-Site Sampling

While there is broad agreement that sampling would probably be employed during a challenge inspection, which is premised on suspicions of cheating, the authority to sample during a routine inspection is one of the most contentious issues regarding the monitoring of the BWC. To serve as a legitimate verification tool, a detailed protocol for all aspects of taking, packaging, labeling, storing, transporting, and testing samples must be articulated, with an assured chain of custody. All tests employed must be validated and conducted by certified laboratories.[25] This protocol must also include safeguards in the event that something goes wrong with the sampling and testing process. With the cooperation of host facilities during trials, industry experts propose to escalate the use of sampling gradually so that such protocols can be developed and tested to the satisfaction of industry and the inspectors.

The industry experts revised their original inspection hypothesis sampling of anything other than a final product would not be allowed during a routine inspection. Previously, they designated sampling as "a tool of last resort" for challenge inspections alone. After further consideration, [26] the industry experts stipulated that sampling would also be a last-resort tool during routine inspections. "Sampling is a great idea," noted one of the experts. "Its effectiveness for virulent solutions is much harder, but if you have a sample

[24] Dr. George Robertson, Ph.D. in molecular biology and vice president for the science and technology division of the PDA, 17 June 2004.

[25] "For anthrax to be taken properly, it has to be analyzed by a person certified to do that analysis—not inspectors in most cases." Furthermore, this industry expert continued, if a sample is taken, it must be tested for a specific reason. "If you think it's anthrax, that's what you test it for using the certified method. You don't test it for tularemia. You don't test it for B*rucella*. You don't test it for pox. It's not a fishing expedition." Dr. George Pierce, professor of applied and environmental microbiology and 20-year plus veteran of U.S. industry, 17 June 2004.

[26] One industry expert advocated using due diligence sampling to verify the facility's declarations, regardless of whether overt suspicions were raised over the course of the inspection. "You should be prepared to take samples just to ensure that they're telling the truth, that what they say is in that fermenter is actually in that fermenter." Dr. Kenneth Coleman, 17 June 2004. Dr. Coleman, Ph.D. in microbiology, is head of the Clinical Microbiology Group at AstraZeneca and a 30-year industry veteran.

and you come up with something, it's the blue dress."[27] The characterization of sampling as a last-resort tool means that inspectors retain the right to sample during a routine inspection, but would exhaust all other means of investigation to resolve questions and inconsistencies before turning to sampling. Totally precluding sampling during a routine inspection would be like "doing a tax audit without having a tax return. It just doesn't make sense not to have the team have the ability to sample at some point."[28] Inspectors may be able to resolve some concerns by reviewing a facility's environmental assessment logs. However, in the event that they have to utilize this last-resort tool, the industry experts wanted the inspectors to create a tentative sampling plan should serious compliance concerns arise that cannot be settled otherwise. A tentative sampling plan might include sampling intermediaries of the final product, air filters, waste disposal systems, or other areas.

For the first trial and during any routine inspection of a manufacturing facility, the only sample automatically taken would be of a final product. The industry experts consider confirming the identity of the product as vital to achieving a principal monitoring objective, determining that the company is making the stated product.[29] Box 10 contains the industry experts' proposed protocol for taking, handling, and shipping this sample. This protocol addresses several factors, but some aspects (e.g., proper temperature and humidity for sample storage and shipping, specific analytical test(s) to be conducted) cannot be specified until the product to be sampled is known. Trial organizers will work these details out in advance with host companies. With regard to step number seven in the protocol, the wording on the form should allow no room for interpretation or other gray areas. If the chain-of-custody form specifies that the sample will be tested for substance "X," it cannot be subsequently tested for "Y."

Box 10: Final Product Sampling Protocol

To verify that the company is making the product(s) it declares, a final product sample will be taken using the following procedures to help ensure the security, integrity, and validity of the sample:

1. From product that is packed for consumer use, the inspectors will select a sample at random or oversee the selection by appropriate facility staff. If the product is packed in very small quantities (e.g., ≤ 10 milliliters or ≤10 grams), frozen, or lyophilized, three packages will be selected from the same lot.
2. A sample selected from product already packaged for consumer use will be identified by lot and ID number. The inspectors will then re-stamp the sample package(s) indicating it is not for sale or for human use.
3. The sample should be split into three aliquots. The inspectors should specify the volume of sample required for testing, and the host should provide three sterile sampling containers.

[27] This comment, of course, refers to the infamous blue dress that President Bill Clinton's paramour Monica Lewinsky kept. Dr. Robert Goldberg, Ph.D. in medical microbiology with over 30 years experience in research and industry, 18 June 2004.
[28] Ibid., 17 June 2004.
[29] "How can we determine we did our job if we don't do that? How can we answer the prime question: are they making what they say they're making? That's number one. Now, are they making anything else? That's why the inspection team is there." Ibid., 8 March 2004.

Box 10: Final Product Sampling Protocol (continued)

4. Inspectors will clearly label and identify each of the three sub-samples. Barcodes may be used for this purpose. To provide an added layer of security, an additional seal will ensure that the sample has not been opened or tampered with in transit or in storage.
5. Samples will be stored according to the parameters (e.g., temperature, humidity) that the host specifies.
6. The disposition of the samples is as follows: 1) one portion for analysis at a certified laboratory; 2) one portion to be archived by the host; and, 3) one to be archived indefinitely under agreed proper conditions in a lockbox at the host facility. This lockbox is to be opened only by mutual agreement of the inspectors and the host facility and therefore would be closed with a dual-key lock and tamper-proof seal to denote unauthorized access. The host facility and inspectorate are each to retain a key. Should the uncertainty that prompted the sampling be resolved to the satisfaction of all parties, the lockbox sample is to be destroyed.
7. The sample must be accompanied by a detailed chain-of-custody form that articulates the people authorized to send, ship, and receive the sample. This form will also stipulate what type(s) of analysis can be preformed on the sample. *Only* the specified method(s) of analysis will be used. The host site, as the shipper, will retain a copy of this form, while another copy will accompany the manifest necessary for the outside of the package.
8. The host should provide the shipping container and materials, which must be approved for the safe and secure sample transport and assure that the packaging will not degrade or otherwise contaminate the sample. If the host facility does not have suitable shipping materials and containers, inspectors will retrieve the needed items from their shipping kit.
9. With host officials observing, the inspectors should package one sample for transport to a designated independent certified analytical laboratory. The shipping regulations of the International Air Transport Association will apply, with the following modifications. The sample will be placed in a sealed, tamper-resistant container. The interior shipping label will include the name of the organism, including genus and species. Should the sample include a select-list agent, a code for the agent will be used on the exterior shipping label to safeguard against theft or diversion of a dangerous pathogen.
10. The package will be shipped through a private carrier, such as Federal Express, rather than the U.S. Postal Service.
11. In the event of an accident involving possible leakage of the sample while in transit, standard decontamination procedures for that organism should be followed, while the person(s) whose name(s) appear(s) on the manifest would be contacted. The inspection team leader and an individual from the host facility would both be designated as points of contact.

Should a non-product sample be required, a specialist from the host facility would take the sample under the watchful eye of inspectors, following agreed protocols, which would be developed for different types of sampling situations. Box 11 provides such a protocol, one for taking in-process samples. Other sampling protocols would take a similar approach, but would have some distinct characteristics depending on the location and type of sample to be taken (e.g., wipe sample from an equipment gasket, air filter sample). The in-process sampling protocol would stipulate, for instance, that the sample be labeled *in-process*, with a final product lot or ID number. To ensure the contents remain secure and identifiable, inspectors would affix a tamper-proof barcode to all sampling vials.

Box 11: In-Process Sampling Protocol

When the inspection team believes that an in-process sample is required to verify the material being produced, the following procedures will help ensure the security, integrity, and validity of the sample:

1. The inspection team leader should immediately request that host personnel to take three identical samples using their standard operating procedure.
2. The inspectors should specify the volume of sample required for testing, and host officials should provide three sterile sampling containers.
3. Once a sample has been requested, members of the inspection team should stay near the vessel being sampled to observe and document in writing all aspects of the sampling procedure.
4. The inspectors should label each sample, seal the tops with tamper-proof seals and identifying barcodes, and place each sample in a sealable biohazard bag.
5. One sample should be packaged by the inspectors for transport to a designated independent certified analytical laboratory. The same shipping and transport procedures used for the final product sample, given in Box 10, should be employed.
6. One sample should be retained by the host for their testing.
7. One sample should be packaged in a sealed container, marked as "certified," and archived in a lockbox at the host facility to be stored indefinitely under agreed proper conditions. This lockbox is to be opened only by mutual agreement of the inspectors and the host facility and therefore would be closed with a dual-key lock and tamper-proof seal to denote unauthorized access. The host facility and inspectorate are each to retain a key. Should the uncertainty that prompted the sampling be resolved to the satisfaction of all parties, the lockbox sample will be destroyed.

Because samples can provide hard-to-refute proof of legitimacy or cheating, the industry experts recognized that sampling protocols must be designed with the utmost care so that inspection objectives can be achieved and host facility concerns addressed. During trials, several aspects of the proposed sampling protocol will be closely evaluated. For example, the concept of using a lockbox may not stand up to scrutiny. If the sample is a perishable biological, a facility might expose the lockbox to heat, radiation, or gaseous sterilization to destroy the sample(s). Therefore, trial inspections may point to the wisdom of requiring the archived sample to be stored at an independent location agreeable to the host facility and the inspectors.[30]

The industry experts agreed that host officials should be encouraged to offer the inspectors all possible alternatives to having to resort to sampling. For example, host officials can provide additional on-site access and more in-depth documentation to help resolve ambiguities. However, should such access not settle the inspectors' concerns, the industry experts stated that companies would be well advised to allow sampling according to agreed protocols. "If they don't let inspectors take the sample and resolve it,

[30] In that case, the sample would be stored under the appropriate environmental conditions and with the appropriate chain-of-custody and security precautions.

then the inspection report is going to look pretty messy," said one industry expert.[31] U.S. industry facilities are accustomed to taking some extensive steps to clear up issues to the satisfaction of U.S. regulatory authorities. In the end, U.S. companies will place a high premium on receiving a clean bill of treaty compliance health from inspectors.

The Inspectors' Post-Tour Evaluation

At the conclusion of the initial tour, the inspectors will individually complete an evaluation form, shown in Table 6, to assess the facility systematically. A rating of "0" indicates nothing is inconsistent with standard scientific or business practices or other pre-inspection expectations. A "1" rating indicates an inconsistency or ambiguity needing further clarification. If an inspector did not see, hear, or read anything germane to a specific category, then the rating would be not determined, or "N/D." Or, if a particular category does not apply to the facility, then an inspector would rate that as not applicable, abbreviated as "N/A." For example, the category about degree of concern about product integrity is not likely to apply to a process in the development stage.

The team leader will tally the inspectors' individual ratings, separating out areas of agreement and disagreement among inspectors. Should all inspectors agree that certain areas appear to be in order, no further discussion would be required. In the event that some or all inspectors issue 1 ratings, the team leader would ask them to state their observations and concerns. The views of team members with expertise in the area under discussion would be given particular weight, though no one's views would be ignored because different inspectors will have observed and heard different things during the tour.

Based on this team-wide consultation, the team leader will establish priorities for subsequent phases of the inspection. Each inspector will be assigned responsibilities for documentation review, interviews, and additional examination of parts of the facility, as needed. Their responsibility will be to further investigate uncertainties and inconsistencies. Should all of the inspectors have rated all areas of a facility with zeros, then the inspection would flip into what the industry experts call "due diligence" mode. The industry experts believe the inspectors would be derelict in their duties if they did not examine certain facets of a facility thoroughly even if everything looks to be on the level after the initial site tour. Table 7 lists the areas identified for due diligence inspection of development and manufacturing facilities. The experts emphasized that the inspectors must execute their responsibilities with the same level of detail and quality as if they were really investigating inconsistencies. In due diligence mode, inspectors will proceed with document review, interviews, and cross-checking only in the areas listed in Table 7.

[31] Dr. Kay Noel, Ph.D. in biophysics and a consultant for biotechnology and healthcare companies with over 20 years of industry experience, 17 June 2004.

Table 6: Inspector Evaluation Form for the Initial Site Tour[a]

	Pre-Tour Document Review[b]	Initial Tour Visual Observations	Initial Tour Interaction With Staff[c]	Initial Tour Overall Rating[d]
Facility:				
• Level of containment				
• Heating, ventilation, and air conditioning system				
• Waste handling, treatment systems				
• Construction materials				
• Cleanliness/ environment				
Product:				
• Microorganisms on site				
• Media on site				
• Equipment				
• Downstream processing				
• Degree of concern with product integrity, quality				
• Levels of inventory and work in progress				
Test Labs:				
• Microbiology labs - microorganisms on site - media on site				
• Animal facilities - routine tests - special models				
• Medical facilities				
People:				
• Organization chart				
• Training				
• Level of cooperation				
SUBTOTAL:				

[a] Each area can be rated individually. Each inspector evaluates the level of consistency of what he or she read/saw/heard with what would be expected of normal scientific and business practices for a facility's declared activities. The evaluation is working only from the information officially given to the inspectors in the facility's declaration. Possible ratings are No Concern (0), Concern (1), Not Determined (N/D), and Not Applicable (N/A). Scores can be tallied both across and down the table for individual inspector. They also can be summed and compared across different inspectors to help identify reasons for different impressions and focus subsequent inspection activities. Higher scores will identify areas where what was read/seen/heard was not consistent with expectations.

[b] Refers to the inspectors' review of required documents prior to site tour.

[c] Includes questions asked during the tour and such factors as ease of facility personnel with their jobs.

[d] Captures the initial document review, visual, and verbal observations.

Otherwise, the inspectors will investigate a larger number of inconsistencies, prioritized according to the cumulative point totals from the inspectors' rating process. Initially, the inspectors will just request certain documents and ask neutrally phrased questions to do so, seeing what light such inquiries shed on the issue. The inspectors could go right for the "kill," so to speak, but doing so might cause a host facility attempting to cover up cheating to begin obfuscating matters. If clarification does not occur, then inspectors will begin pointing out the inconsistencies to the facility operators. At that juncture, the facility "better have a good story," said one industry expert. "The inspectors should ask the right questions to get the story," another swiftly added.[32]

Table 7: Areas of Inspection Focus in Due Diligence Mode

Development Facility	Manufacturing Facility
• Product type(s) and quantity(ies): o Batches o Raw materials ▪ Media ▪ Master stocks ▪ Working stocks • Air handling systems • Equipment	• Product type(s) and quantity(ies): o Batches o Raw materials • Air handling systems • Equipment

The Document Review

According to the industry experts, all facets of the inspection are important to illuminate what a facility is doing, but the document review is really the lifeblood of the inspection because it has the potential to reveal and explain so much. Review of documentation is a natural next step following a facility tour. Of a tour of a European facility, one of the industry experts recalled:

> When I asked about all of these raw materials that did not jibe with the products being manufactured, they told me it was a whole other product line that was not being produced at the time. Just by walking through, you can learn such things as how the amount of products they had kind of corresponded to their number of shifts and what they said they could produce. Just doing a quick inventory and multiplying is very, very useful. Then, asking for the records that match what you see is another way to validate that they are, indeed, on the up and up.[33]

Due to regulatory requirements, U.S. industry facilities will have no shortage of documents to examine.

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[32] Dr. George Pierce, professor of applied and environmental microbiology and 20-year plus veteran of U.S. industry, 8 March 2004; Dr. Jennie Hunter-Cevera, Ph.D. in microbiology and president of the University of Maryland Biotechnology Institute, 8 March 2004.

[33] Dr. Jennie Hunter-Cevera, Ph.D. in microbiology and president of the University of Maryland Biotechnology Institute, 8 March 2004.

The industry experts considered the document review from the perspective of inspectors as well as of a facility trying to conceal evidence of banned activity. As a chemical industry expert said, "With the chemical weapons [treaty], we thought totally cooking the documentations would be very hard thing to do. Somewhere they're going to slip up in the documentation, and that's probably where inspectors are going to find out who isn't running a proper ship. We felt the documentation was critical."[34] The tendency is to assume that "ever since they got Capone for tax evasion, no bad guy keeps good records anymore. If they're going to do something bad, the first thing they're going to do is rig the documentation, and that's the big hole."[35] Cheaters may certainly try to cook the books, but history reveals military organizations in particular and bureaucracies in general to be prolific record keepers. One of the pharmaceutical industry experts observed, "Even if they are making a weapon, it becomes very much document dependent. They need to record what they have done so they can do it again. The records really mean something more as they get more and more into the development side."[36] For this reason, the experts came up with a very lengthy list of documents for the inspectors to analyze. Recognizing the industry's concerns about the sensitive business information in these documents, the industry experts also incorporated certain rights for inspected companies to protect their interests unrelated to BWC compliance (e.g., redaction).

The inspection team will review and analyze documentation in relation to what they observe during the site tour and through personnel interviews. Underlying this phase of the inspection is the assumption that falsifying or manipulating the entire written record would be extremely difficult—but not impossible—for a company secretly developing or producing biowarfare agents. The documents that the inspectors will review on site are numerous and intentionally overlapping, allowing the team to cross-reference anything questionable multiple times, which makes it harder for the facility to keep a crooked story straight or more convincing that a site is engaged in legitimate activity.

After completing the initial tour, the inspection team will revise their document review strategy to focus on specific areas that warrant deeper examination. The team leader will delegate document review responsibilities to the relevant experts among the inspectors.

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[34] Dr. William D. Carpenter, 8 March 2004. Dr. Carpenter has a Ph.D. in plant physiology and spent his 34-year career at Monsanto, where he retired in 1992 as vice president and general manager for agricultural technology. From 1978 to 1994 Dr. Carpenter represented the Chemical Manufacturers of America in the Chemical Weapons Convention negotiations. "How would I hide [anthrax]?" recounted one expert. "There are certain ways that the people around this table might beat the inspectors at their own game. That's why you have this very, very detailed list" of documents to make it much more difficult for anyone to get away with that. Dr. Jennie Hunter-Cevera, Ph.D. in microbiology and president of the University of Maryland Biotechnology Institute, 8 March 2004.

[35] Dr. Robert Goldberg, Ph.D. in medical microbiology with over 30 years experience in research and industry, 18 June 2004. Al Capone was the notorious gangster who dominated Chicago's criminal underworld during the Prohibition era. Responsible for crimes ranging from murder to bootlegging, Capone was finally sent to jail on charges of tax evasion after a special investigator for the Internal Revenue Service found a ledger linking Capone to illegal gambling profits he had never declared as income.

[36] Dr. George Pierce, professor of applied and environmental microbiology and 20-year plus veteran of U.S. industry, 17 June 2004.

All inspectors should share in some of the document review process, as "the devil is always in the details, and you really want multiple eyes looking at this stuff. You don't want [one person] to spend a whole lot of time in any one component sitting down because you go brain dead."[37] During the document review phase, skilled, astute inspectors would probably uncover a facility's trade secret(s).[38] Otherwise, the industry experts concurred, "they're the wrong inspectors."[39]

Companies may be wary about the document review, but they should also appreciate that knowledgeable inspectors will find ample evidence that their facility is legitimate. For example, through the documents pertaining to raw materials and their use (e.g., bill of materials, batch records, strain list), the inspectors can gain insight into matters central to treaty compliance. "There are certain things [about] certain biological warfare agents that you could pick out by the type of material or who made it, in the sense of the ingredients," explained one industry expert. "Those skilled in the art would be able to know that, no, you're not really using this to grow B.t. [*Bacillus thuringiensis*] or to grow anthrax."[40]

Therefore, during a real inspection and a trial inspection, the industry experts agreed that the host site could redact sensitive information not related to the purposes of the inspection from the documents that inspectors review. The inspectors would not be allowed to photocopy the material or take documents off site, unless the host specifically grants permission. Any documents to be taken off site would be marked "confidential," and the inspectors must have the proper procedures in place for handling sensitive documents. The inspectors' intensive review of documents would likely continue throughout the inspection.

A company being inspected should anticipate that the inspection team will request certain documents and would be well advised to pull those documents ahead of time, not only to expedite the process, but also to demonstrate its cooperation. For trial inspections, the organizers will have given the host company a profile of the documents that the inspectors would like to see. To make the trial a reasonable test but manageable for host facilities, documents must cover at least the previous year for the trial inspection. As needed, host facilities will hopefully agree that the inspectors can access historical documents back three years.[41] During a real inspection, the document review would automatically go back three years, but could date back even further if inspectors cannot resolve inconsistencies. During either a real or trial inspection, facilities may opt to redact requested documents and/or provide inspectors with alternative means to answer a

[37] Ibid., 18 June 2004.
[38] Note that should inspectors come across trade secrets, they will be bound by a confidentiality agreement.
[39] Dr. Jennie Hunter-Cevera, Ph.D. in microbiology and president of the University of Maryland Biotechnology Institute, 8 March 2004.
[40] Ibid. *Bacillus thuringiensis* (B.t.) is a rod-shaped soil bacterium that is toxic to certain insects yet harmless to mammals. In 1989, scientists begin using B.t. proteins to develop insect-resistant crops. See www.biotechterms.org.
[41] Many facilities archive older documents off-site, so accessing older records places an additional burden on the host facility. The trial inspection team would only press for such access if it found discrepancies in more recent documents.

point of concern for the inspectors.[42] One expert said, "if you're not getting all the HVAC [heating, ventilation, and air conditioning] information, a good engineer can just look at the system and, bingo, make an evaluation. He doesn't need the records."[43] So, when records are unavailable, inspectors may be able to settle an inconsistency with a closer examination of the facility. Throughout the inspection, both host companies and inspectors will be faced with choices.

To make hosting a trial a more workable proposition for companies, the industry experts prioritized the documentation. For the trial, the group decided that the inspectors would focus on the three or four most important documents that pertain to equipment, materials, operations, and personnel. Table 8 identifies primary and secondary documents in each of the categories. The primary documents are considered crucial to understanding the full picture of the facility's operations, while the secondary documents provide a useful supplement. The team may decide during the inspection that some secondary documents may actually be of primary importance, and vice versa. Therefore, these categories are intended to provide general guidance. Documents in the secondary category that are in *italics* type are those that the industry experts considered to be of primary importance for the inspection, but bumped to secondary status for the purposes of the trial. Should the trial inspectors need further clarification, the host facility would agree in advance that they could conduct a deeper review to include the secondary document to cross-reference information gathered throughout the inspection.

Categorizing and prioritizing the documents in advance will help the inspectors concentrate their efforts. However, sorting through this mountain of cross-linking documents will still be a challenging task. With so many overlaps between different documents—the bill of materials, product disposition records, warehouse records, billing, purchasing, sales, shipping, and receiving records all pertain to what goes in and out of a facility—the inspectors are bound to find some things among the documents that raise eyebrows. "No operation runs perfectly. Mistakes and deficiencies occur, like in biosafety, waste management, et cetera. The whole thing is to show institutional control and compliance, so if those records aren't there, the corporate structure is not trying to monitor what goes on at the plant."[44] Inspectors with a sound understanding of industry operations will know that should they encounter a perfect set of documents, they should beware of possibly cooked books.

[42] Companies should not consider the option to redact an invitation to black out entire pages, the equivalent of the infamous 18.5-minute gap in secretary Rose Mary Woods' tape of President Richard Nixon's conversation with H.R. Haldeman, his chief of staff. Rather, host officials are to make judicious use of redaction, masking only the bare minimum of words.

[43] Dr. Robert Goldberg, Ph.D. in medical microbiology with over 30 years experience in research and industry, 8 March 2004.

[44] Dr. George Pierce, professor of applied and environmental microbiology and 20-year plus veteran of U.S. industry, 8 March 2004.

Table 8: Content and Strategy of the Documentation Review

Equipment Documentation	
Primary Documents	**Secondary Documents**
• Equipment log • Engineering control records: o Biosafety cabinets o Autoclaves	• *Engineering control records:* o *Heating, ventilation, and air conditioning system* o *High efficiency particulate arresting filters* o *Equipment validation/calibration records* • *Airflow diagrams* • *Service contracts*
Materials Documentation	
Primary Documents	**Secondary Documents**
• Strain inventory and use • Product disposition records	• Receiving documents • Billing records • *Warehousing records* • *Bill of materials* • Purchasing records • *Sales records*
Operations Documentation	
Primary Documents	**Secondary Documents**
• Batch records (including procedures and validations for product-release tests) • Laboratory notebooks • Activity log • Quality assurance, quality control paperwork (includes change control and non-conformance reports) • Cleaning logs	• Engineering control documents • *Quarterly environmental records* • Material safety data sheets • Visitor logs/gate records • Project records • Patents • Emergency response SOPs • Internal review committees[a] • *Engineering control records:* o *Hazardous operations records* o *Decontamination operations* • Utility expenditure records (water, energy)
Personnel Documentation	
Primary Documents	**Secondary Documents**
• Personnel records (including turnover records) • Staff lists with titles • Organizational charts	• Employee vaccination records • *Training records* • *Timesheets*

[a] Note that the industry experts recognize that facilities consider certain documents, such as internal review committee documents, so sensitive that facility managers will be very reluctant to have inspectors review them. Documents from a facility's Internal Review Board, Biosafety Review Board, and Institutional Animal Care and Use Committee could assist inspectors.

If a facility is cheating and realizes that inspectors are catching on, host officials may balk at providing inspectors with certain documents. The site might claim that inspectors are not authorized to view proprietary records or dispute the validity of the confidential disclosure agreement that the inspectors have signed. In response, the team leader could propose that the facility officials redact sensitive text and then give them the requested documents. A legitimate company should find redacting documents "perfectly acceptable. On the FDA website, the proprietary information is taken out, but you still get a feel for what you need to know."[45] The inspectors could also ask to view secondary documents that could provide similar information. However, a facility might also claim that the requested records do not exist, which inspectors know is unlikely to be the case. "A research facility with no lab notebooks makes no sense. By definition, they have to have some sort of records."[46] One group member argued that a facility's refusal to provide documentation would itself be incriminating. "If they are not going to produce the documentation, to me that would be sufficient cause for booking them because they're not complying, and they haven't operated in a professional scientific manner."[47]

After completing the document review, the team leader will convene the inspectors to consult with each other about the discovery of new inconsistencies or the resolution of old ones. The inspectors would make note of any suspicions that a site tried to conceal evidence of under inflated claims of protecting proprietary information. As they did after the initial tour, the inspectors' evaluation will be guided by the relevant column in the form shown in Table 9. Areas rated 1 will receive even more emphasis during the interview phase of the inspection and perhaps deeper targeted document review as well. Discussion among inspectors will reveal how to sharpen the lines of inquiry for areas that continue to be investigated.

Interviewing Activities

The initial site tour will include casual, but still purposeful discussions with facility staff. One major tool at the disposal of inspectors to explore and perhaps resolve any inconsistencies with standard and expected practice is additional interviews. If a facility does not make requested personnel available for interviews, the inspectors would consider it an ominous sign. The formal interview phase of the inspection will be marked by sit-down discussions but is also likely to include additional talks with staff on the production line or in laboratories. Inspectors will probably use the former type of interview with senior plant managers and scientists, while the latter might occur with rank-and-file staff, as needed. If inspectors encounter difficulties gaining access to compliance-relevant information, the industry experts recommended interviewing right away certain individuals who will or should know everything about the facility and its operations. The top brass may not always be the most knowledgeable about the site. The inspection team would be working from interview questions drawn up during the pre-trial

[45] Dr. James Poupard, 18 June 2004. Dr. Poupard, Ph.D. in the history and philosophy of science, is president of the Pharma Institute of Philadelphia and has over 40 years of experience in the pharmaceutical industry.

[46] Dr. Kay Noel, Ph.D. in biophysics and a consultant for biotechnology and healthcare companies with over 20 years of industry experience, 18 June 2004.

[47] Dr. Ian Critchley, 18 June 2004. Dr. Critchley is senior director of microbiology at Replidyne, Inc. with over 15 years of industry experience and a PhD in microbiology.

tabletop exercise and refined after the site tour and document review. A fundamental line of inquiry will be whether the workers know what somebody with their responsibilities should know.

The industry experts believe the inspectors should adopt an interview approach modeled after Israeli security forces, where interviewees are subject to multiple lines of questioning by different officials at different times. In Israeli airports, each passenger is asked the same set of questions by two different screeners, who then compare the responses while the passenger is being watched on camera for telltale signs of discomfort.[48] The industry experts agreed that on some key issues, questions should be asked thrice for extra depth. This "good cop/bad cop/worse cop" tactic, as it was dubbed, can be effective in detecting deceptive and intentionally misleading statements. At the very least, it will provide the inspectors with more information than standard, single-person interviews.

Given how productive the triple-questioning tactic can be, the industry experts agreed that the team leader should delegate pre-assigned roles and questions to the inspectors from the initial site tour and onward through subsequent formal and on-the-floor interviews. When properly executed, this multiple-touch tactic should feel casual and natural to those being questioned so that people do not realize that they are getting the second question. The results of using this technique can be "intriguing," said one expert who had plied it. "Sometimes you actually get more detail when a second person asks the question because they [the interviewee] feel that maybe they didn't explain it well to the first person."[49] Of course, the same question can also be posed of multiple employees to allow inspectors to compare answers.

Throughout interviews, the industry experts also noted the importance of observing body language—of both the interviewee and senior manager observing the interview—to ascertain whether the subject is answering truthfully. For this reason, the group agreed that in addition to basic auditing training, a professional inspector corps should undergo required training from a criminal psychologist who can help them discern on the subtle signs that someone is not telling the truth. Inspectors will need to be able to sort out ordinary nervousness from signals of lying, so it is very important that they have a firm grip on the nuances of human communication if interviews are to be maximally effective.

The industry experts expect virtually every company inspected to exercise the right to have a senior manager present at formal interviews. Ideally, the company would not elect a lawyer for this task. While the company needs assurance that the inspectors are not straying off course and its employees are not divulging inappropriate information, a

[48] Dr. Jennie Hunter-Cevera suggested using this approach, to the concurrence of other industry experts. For more on Israeli airport security strategies and procedures, see Harvey Simon, "U.S. Urged to Look at Israel as Model for Airport Security," *Aviation Week's Homeland Security and Defense* 1, no. 15 (6 February 2002): 7; John Croft, "Israeli Security Experts: Technology Not the Answer," *Aviation Week and Space Technology* 155, no. 22 (26 November 2001): 68.

[49] Dr. Jennie Hunter-Cevera, Ph.D. in microbiology and president of the University of Maryland Biotechnology Institute, 18 June 2004.

senior manager can exercise reasonable judgment on such matters. Having a lawyer present could bog down the interview process.

At the conclusion of the formal interview phase, the inspection team would compare and analyze their notes in the context of broader inspection findings. The inspectors should also factor the host officials' level of cooperation with interviews into their assessment, once again guided by the evaluation form shown in Table 9. Inspectors will parse the nuances and insights gained during their interviews, putting some inconsistencies to bed and perhaps identifying others as continuing areas of concern. Even more intensive scrutiny will be given to areas still rating 1 as cross-checking activities commence.

If the inspection team was unable to sort out some inconsistencies by the end of the inspection, then the inspection hypothesis provides for inspectors to interview individuals off site, such as former employees, neighbors, contractors, and others regularly interacting with the facility.[50] Interviewing people not officially part of the facility could be somewhat problematic, however. Former employees may hold a grudge against the company. Neighbors may not be credible or reliable sources of information. Contractors would likely be hesitant to be interviewed because "they want work. If word gets out that they're tattling, they're going to lose their contracts."[51] The industry group recognized the added complexities of interviewing people off site, but decided that it was still important to exercise this option during trials. Rather than make assumptions about the acceptability of off-site interviews, the industry experts suggested that trial organizers solicit the host company's views on how best to accomplish this task during the pre-trial tabletop exercise. The inspected site would be under no obligation to facilitate off-site interviews. Similarly, off-site interviewees would be under no obligation to talk to the inspectors. Should they cooperate, interviewees would have the right to remain anonymous. All off-site interviews must be directly pertinent to further elucidate the inspection and should not be conducted as a fishing expedition where inspectors aggressively aim to uncover discrepancies.

Cross-Checking Activities

The industry experts designed an inspection strategy that is multi-layered and intentionally repetitive in places—especially in the documents reviewed and the questions posed of facility personnel. Cross-checking is a deliberate application of redundancy within and across the monitoring tactics from the outset of the inspection. A certain piece of information noticed during the pre-inspection review of open source materials as somewhat unusual can be a focal point to cross-check when inspectors first walk through the facility. So, during the pre-inspection phase, the inspection team will start a list of areas/information that require a deeper level of investigation. This cross-check list would be dynamic, with the team making changes and additions throughout the inspection to corroborate information or investigate uncertainties. As one industry veteran stated, cross-checking is "the whipped

[50] In comparison, inspections under the Chemical Weapons Convention do not have a provision to enable off-site interviews.

[51] Dr. Robert Goldberg, Ph.D. in medical microbiology with over 30 years experience in research and industry, 9 March 2004.

cream and cherry on top to validate [the facility's] activities."[52] Cross-checking should allow the team to confirm particularly important facts, to explore the reasons for inconsistencies, and to help inspectors assess whether the facility's activities make sense from an operational, scientific, and financial perspective. Cross-checking information will enable the inspectors to develop a more complete and accurate picture of the facility's activities.

Personnel at industry facilities will understand and probably encourage this deeper level of validation to prove beyond a doubt that their activities are legitimate. "It's kind of like when you go out to eat and the restaurant has this statement that reads they are 'determined to be adequate,'" said one industry expert. "I ask, 'Adequate? Do I want to eat here?' If that's the best you can do, it does not build confidence."[53] In other words, the inspectors can accept the first indication about a particular aspect of a facility's operations or they can cross-check that piece of information with other data sources.

Because the inspectors may be working solo at times, the team would meet at least once a day to compare notes, identify areas where the inspectors are confident that activities line up with expectations and standards, discuss remaining inconsistencies, and provide input on areas needing additional cross-checking. Working from this list, the team leader would assign specific inspectors to perform cross-checking tasks, which could include examining three types of documents, asking five questions of several personnel working in a particular area of the facility, and taking a second, more deliberate look at particular parts of the facility, perhaps asking for personnel there to demonstrate a couple of standard operating procedures. Table 9 shows an evaluation form, very similar to one used after the initial on-site tour, that inspectors will use on a daily basis to keep track of their assessments in all areas of the inspection, including cross-checking activity. Essentially, the inspectors will keep returning to the well, so to speak. For U.S. industry facilities, one would expect that eventually all of their ratings in this table would turn to zeros, indicating no BWC compliance concerns about the inspected facility.

The industry experts also foresee that in some cases the inspection team and the host facility may come to the point where both sides conclude that nothing further can be done at that time to resolve an inconsistency or ambiguity. At that juncture, the inspectors will make an important judgment call. If the remaining inconsistencies and uncertainties are important but the inspectors believe that they are most likely the result of poor management, sloppy operations, or sub-par science at the facility, then the inspectors may come to consensus that the facility is not well operated but it does not present genuine BWC compliance concerns.[54]

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[52] Ibid.

[53] Dr. George Pierce, professor of applied and environmental microbiology and 20-year plus veteran of U.S. industry, 9 March 2004.

[54] The inspectors purpose is solely to monitor BWC compliance, so other possible regulatory infractions, unless they pertain directly to BWC compliance, will not be discussed in a final inspection report. The reporting process and trial inspection debriefing are addressed in Chapter 7.

Table 9: Inspector Evaluation Form for the Document Review, Interviews, Additional Visual Observations, and Cross-Checks[a]

	Document Review[b]	Visual Observations	Interaction With Staff[c]	Cross-checking[d]	Overall Rating[e]
Facility :					
• Level of containment					
• Heating, ventila - tion, and air conditioning system					
• Waste handling, treatment systems					
• Construction materials					
• Cleanliness/ environment					
Product :					
• Microorganisms on site					
• Media on site					
• Equipment					
• Downstream processing					
• Degree of concern with product integrity/quality					
• Levels of inventory and work in progress					
Test Labs :					
• Microbiology labs - microorganisms on site - media on site					
• Animal facilities - routine tests - special models					
• Medical facilities					
People:					
• Organization chart					
• Training					
• Level of cooperation					
SUBTOTAL:					

[a] Each area can be rated individually. Each inspector evaluates the level of consistency of what he or she read/saw/heard with what would be expected of normal scientific and business practices for a facility's declared activities. The evaluation is working only from the information officially given to the inspectors in the facility's declaration. Possible ratings are No Concern (0), Concern (1), Not Determined (N/D), and Not Applicable (N/A). Scores can be tallied both across and down the table for individual inspector. They also can be summed and compared across different inspectors to help identify reasons for different

impressions and focus subsequent inspection activities. Higher scores will identify areas where what was read/seen/heard was not consistent with expectations.
[b] Refers to the intensive review of a facility's documents.
[c] Encompasses responses of facility personnel to formal and casual interview questions.
[d] Captures the integrated cross-checking of key data points to clarify identified inconsistencies.
[e] Sums scores for the document review, interviews, additional visual observations, and assigned cross-checking of important data points.

Alternatively, the inspectors could have some evidence that a site is attempting to hide covert weapons activities. The ambiguities and inconsistencies remain because the facility has begun to stall, obfuscate, and deny inspectors the access needed to gain a better understanding of the site's activities. Both situations will be reported, the former triggering requests for additional information from the facility and a possible follow-up routine inspection to confirm compliance. The latter situation could flip the inspection immediately into a challenge inspection mode. Chapter 3 discusses the triggering of a challenge inspection.

Chapter 7
Post-Trial Inspection Reporting Activities

Field tests of the strategy and tactics that could be used to monitor the Biological and Toxin Weapons Convention (BWC) at industry facilities will be multi-step endeavors intended to mimic as closely as possible the events that would occur in a genuine BWC monitoring inspection. The industry experts have added three additional steps to the testing process that would not be part of an actual BWC inspection. The initial tabletop exercise, held principally to describe what a trial inspection would entail and answer questions from potential host companies, is the first of those auxiliary steps. The other two extra steps—a meeting for trial inspection participants to express their thoughts and recommendations and a series of activities to share the lessons of trial inspections—are discussed in the latter two segments of this chapter. The host company would be encouraged, but not required, to participate in the introductory tabletop, described in Chapter 5, and in briefings of the trial inspection lessons to interested parties.

This chapter also addresses an integral component of the trial inspection, namely the preparation of the trial inspection report. All totaled, industry experts expect the central trial activities to take approximately eight days. The only host-site participant to attend the two-day pre-trial tabletop exercise, wherein inspectors will review open-source information and tailor their tactics and team membership for the upcoming inspection, will be the observer. A fairly large number of company personnel would be involved in the actual trial inspection, including those who would host and accompany the inspection delegation and those with whom the inspectors might only have passing contact. The estimated time for on-site monitoring activities is five days. In the final stage of the trial, a much smaller number of host company officials need to participate, namely the host company observer and a handful of company officials central to receiving and interacting with the inspection delegation. A larger number of company personnel may, however, wish to hear first-hand the discussion slated to evaluate the trial itself. This portion of the trial activities should last over half a day.

Preparation of the Trial Inspection Report

When the trial inspection wraps up, the team will prepare a draft final report.[1] In a meeting that is still considered to be part of the trial inspection activity, the inspectors will share findings with host site officials, both orally and in a concise, written report. The text of this report is to be as brief as possible, restricted to statements about BWC compliance and associated factual findings. A possible reporting template is the Food and Drug Administration's (FDA's) letters and reports related to adverse actions, which often

[1] The pharmaceutical industry experts patterned these post-inspection reporting guidelines on the procedures used in Chemical Weapons Convention (CWC) inspections. Under CWC procedures, the initial report shared with the host site is labeled "draft" pending its review by the inspectorate headquarters to ensure that the inspection findings are consistent with what has been observed in similar facilities around the world. A final report lists any unresolved matters, including ambiguities, inconsistencies, and violations of a technical or grave nature. The CWC inspectorate issues the final report to the host government.

contain short, bullet-point summaries.[2] Once inspectors review their draft report, the host officials may comment on any uncertainties or discrepancies that the inspectors raised. During this discussion, the host company may provide additional information or documentation to try to put outstanding issues to rest before the departure of the inspectors. While host officials are under no obligation to provide the inspectors with any more data, they may decide it is in their best interests to do so. The draft final inspection report will reflect any unresolved matters. Company officials may also make suggestions about the exact wording of the report, which the inspectors may or may not accept.

In addition to any verbal remarks they make before the inspectors leave, the host site has the right to respond in writing to the content of the inspection report, as well as comment on the competency of the inspection team. The inspection report will include the names of the inspection team members. The response of the host site to the inspection report is to be included in the official inspection record and may be provided during this discussion or after the inspectors leave. Once the inspection report is finalized, the host site will retain a copy of the final report and any attachments, in addition to a copy that is sent to the host government.

The industry experts estimated that the draft report presentation, response from the host officials, and possible revision of the draft report would last roughly two hours, depending on whether the inspectors are given new information. The trial inspection will officially end following this report-drafting activity. However, the entire inspection delegation will remain on site for a few more hours to engage in additional discussions with host site officials.

Review and Evaluation of the Trial Inspection

Once the trial inspection concludes, all of the trial inspection participants—the inspectors, host officials, U.S. government escorts, trial ombudsman, and host site and chemical industry observers—will begin an interactive feedback session structured to solicit observations and lessons from the trial participants. Still fresh from what they have just experienced, trial participants will be asked to provide recommendations pertinent to the road ahead and share their views about what transpired, whether good, bad, or indifferent. Participants will be free to raise matters that were troublesome and give their views on why difficulties occurred. Although the exact agenda for this session will be arranged in advance with the host company, Box 12 provides a draft agenda. Trial organizers and the host company will agree on the timeframes for each briefing, which should be followed by short periods of discussion.

[2] Examples of the FDA's briefer reporting forms can be found by searching the FDA's website for adverse events reports or FDA-483 reports, which detail "objectionable practices or deviations" from FDA regulations, as revealed through FDA inspections. These reports are available online at www.fda.gov.
In the case of a BWC final inspection report, any information supplemental to the brief report would remain confidential, unless the inspected facility gave specific permission for additional information to be released.

Box 12: Proposed Order of Briefings for the Evaluation of the Trial Inspection

- Host company officials
- Host company's trial inspection observer
- U.S. government escorts
- Trial inspection ombudsman
- Chemical industry observer
- Inspection team
  - On-the-record remarks
  - Private remarks
- General discussion about lessons learned
- Discussion of trial inspection report:
  - Content
  - Preparation
  - Approval
  - Briefings and dispersal
  - Press release/event

Host company officials will be the first to offer their thoughts on the trial inspection. They might offer feedback on the tolerability and effectiveness of different inspection techniques and on the role and comportment of the escorts. Host officials will be especially encouraged to make suggestions for the improvement of the inspection hypothesis and for the conduct of future trials. Next, the host site observer, who shadowed the inspection team throughout the entire trial process, will present his or her assessment of the inspection and recommendations regarding the inspection team, the U.S. government escorts, and the facility personnel. Given this individual's status as a staff member of the company and an insider to the discussions among inspection team members, their observations ought to afford considerable insight into the effectiveness and acceptability of the trial, suggesting ways to improve inspection strategy and tactics in future trials.

Following the host company observer, the U.S. government escorts will impart their views about the trial inspection. Depending on its composition, the escort team may be able to compare the events of the trial with actual treaty inspections. The government escorts are likely to voice thoughts about what both the inspectors and the host company did during the trial inspection. The next two briefings will come from the trial inspection ombudsman and the chemical industry observer. Just as with the host site observer, these two individuals should have interesting insights to share, given their experience and neutral vantage points during the inspection.

The inspectors may have made a passing comment about the level of the host company's cooperation during their official briefing of the final inspection report. At this juncture, the inspectors will drop the façade somewhat to give host company officials more extensive feedback on their conduct, including how the company's decisions to share or withhold access and documentation influenced the inspectors' decisions. This discussion will provide an unusual opportunity for the host company to hear the unfettered views of inspectors. If the inspectors saw room for improvement, they would also give the host company officials

recommendations to enhance their policies and procedures to safeguard proprietary information while during inspections and other visits. In the aftermath of this exchange, the host company could well improve its ability to protect its trade secrets while still satisfying the needs of outside inspectors.

At this point, if necessary, the full meeting would recess briefly for a private discussion between the inspection team and host company officials. No other members of the inspection delegation will sit in on this discussion, during which the inspection team will inform host officials of any possible U.S. regulatory violations uncovered during the investigation. The inspectors do not represent any U.S. regulatory agency but their experience naturally lends itself to the detection of regulatory problems.[3] Host officials are not obligated, but would be well advised, to heed their counsel about regulatory compliance. Neither the final inspection report nor the report that summarizes the trial experience and its attendant lessons will include any of the inspectors' observations about U.S. regulatory compliance, unless an infraction also pertains directly to BWC compliance.

Following the briefings, the entire group of inspectors, host officials, U.S. government escorts, the inspection ombudsman, and the trial observers should identify lessons learned for inspectors and hosts and pinpoint specific areas necessary to improve future trial inspections. Recommendations for adjusting the original routine inspection hypothesis for industry sites will also be solicited. This segment of the evaluation is meant to build on the previously shared observations. The lessons learned can be negative, positive, or neutral, but at least they will be educated by events. Much has been said about what will, would, could, might, or should happen during BWC compliance inspections of industry facilities. Observations based in experience will be much more illuminating than speculation.

On the heels of this discussion, the group will talk about how the lessons from the trial inspection will be shared with interested audiences. The industry experts believe that a report summarizing the basic events of the trial and the lessons learned should be prepared. The template for this report is the after action reports prepared following industry trials in other countries, such as the United Kingdom and Brazil. These reports provide a concise summary of the trial inspection objectives, activities, lessons learned, and conclusions.[4] This approach will be broached with prospective host companies in the pre-inspection tabletop exercise as a prelude to preparing a list of questions and objectives relevant to the host company, inspector, and government escort points of view. These guidelines will help all trial participants prepare their contributions for the lessons learned report. Deadlines will be set for the participants to submit their input to the trial organizers.

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[3] Although the trial inspectors are not employees of the U.S. government, the industry experts worried that the inspectors would be legally obligated to report any U.S. regulatory infractions that they might see. To make sure that their recommended approach would not pose problems for the inspectors, the industry experts suggested that trial organizers get legal advice on this matter prior to the first trial.

[4] "Report of a Visit to a Pharmaceutical Research Facility: Working paper submitted by the United Kingdom of Great Britain and Northern Ireland," BWC Ad Hoc Group/WP258 (Geneva: 9 January 1998); "Report of a Joint UK/Brazil Practice Non-Challenge Visit: Working Paper Submitted by Brazil and the United Kingdom of Great Britain and Northern Ireland," BWC Ad Hoc Group/WP76 (Geneva: 18 July 1996).

The host company will not be obligated to make a contribution to the report but will have the right to review it. Once the report is drafted, the host site will have a month for its legal department and top executives to review and make any necessary revisions to the document. One of the objectives of preparing this report is to replace supposition with fact. The industry experts were mindful that host companies would be extremely sensitive about any association remotely linked to the phrase "biological weapons," even if that phrase is immediately followed by such words as "ban" and "nonproliferation regime."

Therefore, the host company can choose to remain anonymous, characterized in terms that will not have it stand out from any of the other numerous similar industry facilities across America.[5] While the industry experts were skeptical that word of the host company's identity would not eventually leak out, most likely from facility employees prone to discuss the presence of inspectors on site, the company itself would still have "plausible deniability" about its participation. Alternately, the host company could elect to acknowledge its role as a trial inspection host, a service that is to be lauded. Companies that decide to host a trial inspection will be helping their industry, their government, and the international community address one of the most worrisome threats to global peace and security, how to stop the proliferation of biological weapons.

Over the course of the following month, the inspection team, government observers, and ombudsman would review the host's changes to the document and negotiate language acceptable to all parties. The resulting report would be the basis for briefings to various interested audiences, as described in the next segment of this chapter, and would be available for public release. Following the trial, the host company would have the authority to release a press statement. Should the host company decide to go public, then professional associations and societies, such as the American Society for Microbiology, could also be approached to issue statements applauding the facility's willingness to volunteer for a trial inspection to advance efforts to create a BWC inspection regime.

In addition to the aforementioned inspection report, trial organizers will prepare a separate document that provides a more in-depth summary of trial activities—a policymaking and training aid for the U.S. industry and government officials. The trial evaluation briefings and discussions will be more candidly related in this report. Of course, the host company's legal department would also review this report, which could be modeled on a report of a trial inspection of U.S. Department of Energy facilities.[6] Again, the host company's identity can be shielded in this document, which would be marked indefinitely as a "draft interim report."[7] Since the report is "draft guidance"

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[5] The industry experts deliberately set broad defining characteristics for potential trial hosts, such as a manufacturing facility with large-scale capacity that works with class 2 or higher organisms. For more, see Chapter 3.

[6] Pacific Northwest National Laboratory, *DOE Exercise to Determine the Potential Impact of a Legally Binding BTWC Regime on DOE Sites*, PNNL-11015 (Washington, DC: U.S. Department of Energy, June 1998).

[7] The model for this two-tiered reporting activity is the FDA's form 483 process. The short form 483 is a public record. FDA inspectors back up the brief form 483 with a lengthier document providing much

intended to inform industry and U.S. government policymaking, changes to that guidance can be anticipated as additional trial inspections unfold. Hence, the marking of the document as "interim" is appropriate. The distribution of this second report will be very restricted.

Post-Trial Activities to Share Lessons Learned

Aside from gaining *bona fide* field experience as to whether BWC compliance can be monitored effectively at industry facilities while not compromising the biopharmaceutical industry's proprietary information, the other central reason underlying BWC trial inspections at industry sites is to educate the industry and U.S. government about whether BWC compliance can be accomplished and, if so, at what cost. To make the trials less demanding on host facilities, this education will take place second hand, via post-trial inspection briefings to share the lessons learned. These briefings will present an overview of the inspection proceedings and outcomes, along with recommendations to refine the inspection strategy and techniques. Target audiences for this briefing would include:

- U.S. government executive branch departments, including Departments of State, Defense, and Commerce and the Intelligence Community;
- Appropriate committees of the U.S. Senate and House of Representatives;
- U.S. biopharmaceutical trade associations;
- Relevant professional societies;
- Other interested nongovernmental organizations; and,
- International audiences, including industry trade associations in Europe, Japan, Canada, and Australia; the United Nations Conference on Disarmament offices in Geneva; and key foreign government delegations.

To ensure that events are accurately conveyed, briefers will work from the essential agreed points contained in the report that is available for public distribution. Unless the company that hosted the trial gives express permission, briefers will not reveal that company's identity.

Ideally, one or more of the actual trial participants would give these briefings. For instance, the U.S. government participants selected as escorts would be responsible for the briefings within the executive branch offices that deal with biological weapons nonproliferation. The industry's two largest trade associations—the Pharmaceutical Research and Manufacturers of America and the Biotechnology Industry Organization—will of course be debriefed, preferably by the host company's trial inspection observer. The industry experts believe that their trade associations need to re-evaluate their position regarding the possibility of monitoring the BWC.[8] Referring to the eventual creation of

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greater detail on the inspectors' observances. Note that interim reports are not subject to Freedom of Information Act requests.

[8] The Pharmaceutical Research and Manufacturers of America (PhRMA) has stipulated that a BWC monitoring regime should consist only of challenge inspections. Otherwise, a private company could opt to invite inspectors to "familiarize" themselves with their facility, but this activity would not constitute a

a BWC inspection system, one industry expert said, "the people who represent the industry are in serious denial and they don't realize it's going to happen," sooner or later.[9] The industry experts would welcome the constructive participation of the trade associations in BWC trial inspections.

Specialized professional societies, such as the American Institute of Chemical Engineers, the American Society for Microbiology, and the Society for Industrial Microbiologists, would also receive post-trial inspection briefings. Many industry scientists are members of these associations, and the industry experts believe their input would foster an even more robust inspection hypothesis and trial inspection process.

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compliance monitoring activity. For more, see PhRMA Board, "Statement of Principle on the Biological Weapons Convention" (Washington, DC: 16 May 1998); PhRMA Board, "PhRMA Position on a Compliance Protocol to the Biological Weapons Convention" (Washington, DC: May 1998); "Summary of PhRMA's Position on a Compliance Protocol to the Biological Weapons Convention" (Washington, DC: July 1998); "PhRMA Position on a Compliance Protocol to the Biological Weapons Convention" (Washington, DC: 9 January 1997); "Compliance Protocol to the Biological Weapons Convention: A Joint Position of European, United States and Japanese Industry" (n.d.). These documents are all available at PhRMA's website at: www.phrma.org.

[9] Dr. George Pierce, 8 March 2004. With a Ph.D. in microbiology, Dr. Pierce has over 20 years of experience in the U.S. pharmaceutical industry and is currently a professor of applied and environmental microbiology at Georgia State University.

Chapter 8
Conclusions

Using the plans laid out in Chapters 3 thru 7 of this report, a group of experts from the U.S. pharmaceutical and biotechnology industry propose that full field trials to test the feasibility of monitoring the Biological and Toxin Weapons Convention (BWC) be conducted. They recommend that the first trial inspection take place at a manufacturing facility because an inspection to confirm that a plant is making its declared product(s) and not biowarfare agents would be less demanding than deciphering whether a biopharmaceutical development site is in compliance with the BWC. The industry experts believe that the initial trial inspections of manufacturing and development activities should be separate. This approach will allow inspectors to gain a better understanding of the capabilities and limitations of the proposed inspection strategy and techniques. Furthermore, trials that focus on distinct activities will be less of a burden for host companies.

The lessons learned from these trials should enable the development of an overall strategy and tailored techniques to monitor industry facilities, which often house development and manufacturing activities at the same site. Trials will allow the inspection teams to work with industry to refine further the proposed inspection protocols for the on-site tour, document review, interviews, examination of strain collections, and sampling and analysis. For a full test of the soundness of their inspection hypothesis, the industry experts suggest that trials be structured so that the inspectors are gradually presented with tougher and tougher situations to assess whether the proposed monitoring techniques will allow the inspectors to detect cheating and cope with less than cooperative host facilities.[1] Deliberate escalation of the difficulty of trial inspections should also enable U.S. industry to gain confidence that the interests of host facilities can be safeguarded even when inspectors have to employ a more aggressive approach to understand whether a facility is engaged in legitimate activity or not.

As they constructed their inspection hypothesis and trial inspection plans, the industry experts struggled to achieve the right balance to empower inspectors to investigate treaty compliance while not endangering the proprietary interests of pharmaceutical and biotechnology companies. However, the issues they wrestled with to devise the detailed proposals contained in this report pale in comparison to the bias standing in the way of creating an effective monitoring protocol for the BWC. The first bias concerns the attitude expressed to date by the U.S. pharmaceutical and biotechnology industry and the U.S. government. Neither is disposed to conduct BWC trial inspections or to reconvene formal protocol negotiations. Should trials be conducted and prove that inspectors can differentiate between legitimate commercial facilities and those masquerading as such, a campaign would be needed to restart international negotiations to add a monitoring

[1] With the permission of host companies, these more advanced trials would incorporate planted "evidence" that the host facility may be engaged in illicit bioweapons activities. In more advanced trials, the organizers would also ask host company officials to test the inspectors' wits and capabilities by deliberately denying them access to some areas of the facility, refusing to provide certain documents, or not allowing them to interview certain staffers.

protocol to the BWC. The U.S. government should re-engage in a sincere effort to achieve that objective. Determined political and technical leadership will have to be exerted if agreement is to be reached. The international community is dubious of U.S. intentions because negotiations were disbanded at the behest of Washington in 2001. Moreover, a focused approach to develop consensus on a protocol will be needed to prevent some BWC members from trying to piggyback distracting issues on a monitoring protocol.[2] Consistent with their step-by-step approach to trials, the industry experts believe that the obstacles closest to home should be tackled first.

Gaining the Cooperation of U.S. Industry

As insiders of the U.S. industry, this group of experts knows first-hand the concerns of U.S. pharmaceutical and biotechnology companies about opening their doors to trial inspections. Aside from the fact that their principal trade associations, the Pharmaceutical Research and Manufacturers of America and the Biotechnology Industry Organization, have not exactly embraced the idea of BWC inspections, one industry expert said that U.S. companies "have nothing to gain and everything to lose" by stepping forward to host a trial.[3] Furthermore, said another, industry executives know they are not in the biological weapons business and may see the BWC "as irrelevant to what they are doing. They are trying to make money and please shareholders and prevent price controls."[4] At first blush, these viewpoints are certainly justifiable.

Thinking more globally, however, those views do not hold up as well. To begin with, the industry prides itself on taking calculated risks for the betterment of mankind. For example, companies invest tremendous resources annually to develop new medications and other products. Similarly, the industry experts are asking companies to invest, without guarantee of any return profit, in efforts to rid the world of the scourge of biological weapons. Seen in this light, the industry's participation is an act of good American and global citizenship, a service for U.S. security and for world peace. These very reasons motivated the U.S. chemical companies and its principal trade association, at that time known as the Chemical Manufacturers of America, to help lead the charge to conclude the negotiation of the 1992 Chemical Weapons Convention and to support its

[2] Just as they have during forums related to the chemical and biological weapons treaties, the neutral, nonaligned countries can be expected to lobby for the dissolution of the Australia Group and the provision of developmental assistance. Statement by Ambassador Shyamala B. Cowsik, Permanent Representative of India to the Organization for the Prohibition of Chemical Weapons Leader of the Indian Delegation to the First Review Conference of the Chemical Weapons Convention (The Hague: 29 April 2003); Statement by H.E. Ali-Asghar Soltanieh, Ambassador of the Islamic Republic of Iran, Opening Plenary of the Fifth Review Conference Of the Biological Weapons Convention (Geneva: 19 November 2001).

[3] Dr. Jim Poupard, 18 June 2004. Dr. Poupard, Ph.D. in the history and philosophy of science, is president of the Pharma Institute of Philadelphia and has over 40 years of experience in the pharmaceutical industry. The Pharmaceutical Research and Manufacturers of America (PhRMA) "is skeptical that any site inspection can detect a violation of the BWC." For more, see "Summary of PhRMA's Position on a Compliance Protocol to the Biological Weapons Convention" (Washington, DC: July 1998), available at www.srpub.phrma.org. PhRMA also states that the "risk to CBI [confidential business information] and facility reputations" does not justify conducting inspections to verify compliance with the BWC. "Proposals for U.S. Implementing Legislation for the Biological Weapons Convention Protocol," Joint FAS/PhRMA position paper (May 2000).

[4] Dr. Frank Malinoski, 18 June 2004. Dr. Malinoski, Ph.D. in microbiology, is executive vice president and chief medical officer of a U.S. biotechnology company and a former inspector in Russia and Iraq.

ratification and implementation. In the latter part of the 1900s, this industry did not make poison gas, but the industry's leaders understood that the past associations of some companies with weapons programs and the inescapable dual-use nature of its facilities would tar the industry indefinitely until treaty inspectors could declare their companies in treaty compliance. Through trial inspections at U.S. chemical plants, the industry learned that treaty inspections would not compromise its trade secrets.[5]

Furthermore, the biopharmaceutical industry's trepidations about hosting a trial inspection may be overblown. The industry experts put together an inspection hypothesis and trial inspection plans fully aware of how vitally important it is for industry to protect its proprietary data. Accordingly, trial inspection plans have many features to ensure that companies can safeguard their interests while inspectors are on site. The following paragraphs briefly discuss these features, which are covered in more detail in Chapters 4 thru 7.

In addition, should U.S. pharmaceutical and biotechnology companies really examine the inspection hypothesis and trial inspection plans, they will find themselves on familiar ground. Box 13 puts the proposed BWC trial inspection practices into perspective with those that the FDA uses. One distinction between the two inspection regimes that should be noted up front is that the FDA inspects only manufacturing facilities, whereas BWC trials would involve manufacturing and development sites. The proposed inspection formula has many commonalities with the practices that the FDA employs, as well as some interesting departures. Some of the differences from FDA practices would probably have no impact on host companies, while others would either make a BWC trial inspection more or less demanding than an FDA inspection.

Box 13: Comparison Between the Proposed BWC Trial Inspection and FDA Inspection Practices

Similarities Between FDA Inspections and BWC Trials
• Inspection team tailored to site • Host site plans, prepares for inspection • All visitors escorted at all times • Inspectors confirm site is engaged in declared activity • Inspectors identify expectations, areas of interest before arrival on site • Host facility provides inspectors with a workroom • Host site moves inspectors about the site in company vehicles • Host facility screens equipment brought on site • Inspectors follow host site biosafety, product protection rules • Host company barred from providing inspectors with gifts, parties, or travel and lodging expenses

[5] The Chemical Manufacturer's Association even became an advocate for the CWC after the conclusion of the seven trial inspections, noting, "industry's confidential business information will be protected." Frederick L. Webber, President and CEO of the Chemical Manufacturer's Association, Letter to the Editor, "We should support the Chemical Weapons Convention" (*Washington Times*: March 6, 1997). In more detail, "Testimony of Will B. Carpenter" *Hearings on the Chemical Weapons Convention before the U.S. Senate Foreign Relations Committee*, S.Hrg 103-869 (Washington, DC: U.S. Government Printing Office, 1994): 88-92, 111-112, 147-150.

Box 13: Comparison Between the Proposed BWC Trial Inspection and FDA Inspection Practices (continued)

<table>
<tr><th colspan="2">Similarities Between FDA Inspections and BWC Trials</th></tr>
<tr><td colspan="2">• Inspectors take initial tour throughout facility, talking with site personnel, taking a final product sample, reviewing contents of strain collection(s)
• Inspectors interview key senior personnel in each division and rank and file, as needed
• Inspectors evaluate level of host site cooperation
• Inspectors discuss findings with host facility, review draft report with them, and give host company opportunity to provide additional data, if necessary, before report finalized
• Host company has the right to respond to inspection report
• No media participation while inspection is underway</td></tr>
<tr><th colspan="2">Differences Between FDA Inspections
and BWC Trials Unlikely to Impact Host Facility</th></tr>
<tr><td colspan="2">• Inspectors confirm no diversion of materials for covert weapons production
• Inspectors confirm site is not functioning as a covert weapons production facility
• All trial participants sign confidentiality agreement
• Inspection ombudsman to observe trial
• Inspectors review extensive open source data before going on site
• Inspectors interview select off-site personnel for additional corroboration
• Inspectors share lessons from trial with interested audiences through briefings, host-approved report</td></tr>
<tr><th>Differences Likely to Make BWC Trial Inspections Less Demanding Than FDA Inspections</th><th>Differences Likely to Make BWC Trial Inspections More Demanding Than FDA Inspections</th></tr>
<tr><td>• Host company vets candidate inspectors, escorts, ombudsman, chemical industry observer
• Host site observer placed on inspection team
• Facility required to declare very limited data in advance
• Host officials lead site tour, can deny access to sensitive areas, but are discouraged from doing so
• Host facility can shroud, but shrouding should be minimal
• Inspectors confirm contents of strain collection via examination of labels
• Document search goes back 1 year, optionally no more than 3 years</td><td>• Inspectors on site approximately 5 days
• Total inspection delegation to include 10 or more people</td></tr>
</table>

The BWC trials have two inspection goals that do not exactly coincide with FDA inspections, namely to confirm that no items are diverted to bioweapons activities and that the site is not serving as a covert weapons production facility. With regard to these inspection missions, FDA inspectors may review logs for the receipt and use of production and testing materials and components, but BWC trial inspectors may look at these materials with more intensity. Except to confirm that a dedicated site is not manufacturing another substance or that a non-dedicated site is not manufacturing

substances that could contaminate the declared product, the FDA is not concerned with "covert" production.

Some differences in practice are unlikely to have any effect on companies hosting a BWC trial inspection. Beforehand, BWC trial inspectors will review a great deal of open source information, but host companies are not required to facilitate its collection. FDA inspectors review only information that the inspected company provides. Although FDA inspectors do not sign confidentiality agreements, all documents they review are considered confidential. BWC trial inspectors will sign confidentiality agreements. While off-site interviews would not impose on host facilities because there would be no obligation to help inspectors with this aspect of a trial, a burden could arise if such interviews affected the positive relationship that host companies have with contractors or others contacted for such interviews. Whether off-site personnel would object to participating in trial inspections is unknown, so trial organizers would consult with host facilities before the trial about how this task could best be accomplished.[6]

Because the industry experts want the lessons from BWC trials to be shared with interested outsiders, they have devised reporting procedures that will protect the host company's interests. Furthermore, the host company can remain anonymous in trial reports, whereas the FDA publicly identifies companies in their reports on adverse events, recalls, and other industry matters. No media would participate in either type of inspection, although members of the press could attend briefings of the lessons learned from BWC trials. The media may consult a host-approved trial inspection report as well as documentation that the FDA makes publicly available.

Virtually every aspect of an initial site tour during a BWC trial inspection would mirror what the FDA does. Similar to their BWC trial inspection counterparts, FDA inspectors identify inconsistencies with their expectations, which are based on regulatory compliance rather than compliance with treaty prohibitions against development, production, and stockpiling of bioweapons. Before arrival on site, the FDA is sent all of the documents that the BWC trial inspectors will only access once they are on site to facilitate the site tour.[7] Both sets of inspectors will ask questions along the way, take a final product sample for confirmation, and identify areas to dig deeper through documents and interviews. FDA and BWC trial inspectors are both supposed to cover all areas of the facility. The FDA inspector's consideration of laboratories and equipment is centered on the tests and equipment specified in regulatory submissions. In touring an animal facility, FDA inspectors would focus on Good Laboratory Practices. BWC trial inspectors are examining these areas with treaty compliance in mind. Both tours would last several hours.

FDA and BWC trial procedures are roughly equivalent in terms of debriefing inspection findings and filing short and long-form reports. The former are public documents (e.g., short form 483), and the latter remain confidential. The host facilities have the right to

[6] To reduce the possibility that working relationships would be damaged, the industry experts agreed that those who consent to off-site interviews could opt to do so anonymously.

[7] For a list of documents that BWC trial inspectors would review prior to the site tour see Box 6, Chapter 6.

respond to both FDA and BWC inspection reports. The competency of BWC trial inspectors is also subject to host comment.

In a few respects, BWC trials are likely to be more of a burden to host companies than FDA inspections. Most FDA inspections last from two to three days, although they can go much longer if inspectors find problems. BWC trial inspectors are likely to be on site for five days. The FDA usually fields two-person inspection teams, but a BWC trial inspection delegation may include four or more inspectors, as many as six government escorts, an ombudsman, and an observer from the chemical industry.

In quite a few respects, a BWC trial is likely to be less onerous than an FDA inspection. Host companies have no say in the individuals that the FDA sends to their site, but will vet all members of a BWC trial inspection delegation. The deliberations of FDA inspectors are private, but the host company can put an observer on a BWC trial inspection team. Data declared to BWC inspectors before their arrival is quite minimal. The FDA requires that a company submit full information in advance on the facility and its manufacturing and testing processes. In a BWC trial, host officials lead the tour and can deny the inspectors access to sensitive areas, if they deem it necessary. That is not the case with an FDA inspection, where the full facility must be available even if inspectors are focusing on a single product. FDA inspectors may specify areas of interest and the order of the tour, with no limitations imposed. Shrouding is allowed during a BWC trial, though facility operators will be encouraged to keep it to a bare minimum. FDA inspectors do not tolerate shrouding. BWC trial inspectors will confirm the contents of a facility's strain collection principally by looking at labels, but FDA inspectors have no limitations in confirming the identity of strains. FDA inspectors can ask for any documents archived, but BWC trial inspectors have prioritized documents to be reviewed to make the trial a reasonable and tolerable test. BWC trial inspectors will review documents dating back only one year in most cases and never more than three years.

In sum, a BWC trial inspection would be a burden, but it would not be an intolerable beast. U.S. pharmaceutical and biotechnology companies will find much of what BWC trial inspectors do familiar because of the aforementioned similarities with the FDA inspection process. The unexpected bonus for companies that volunteer to host BWC trial inspections is that with their own observer on the inspection team, a BWC trial will allow host companies insider access to the inspection process. Moreover, BWC trial inspectors will take additional steps to help host companies sharpen their internal policies and procedures for safeguarding proprietary data.

A Necessary About-Face in U.S. Policy

While the industry experts can understand why U.S. companies might not jump at the chance to host trial inspections, they are perplexed as to why the U.S. government has not proceeded with trials and has all but quit international efforts to strengthen bioweapons nonproliferation tools. The Clinton and Bush administrations have both shunned the requirements of a 1999 law to conduct monitoring trials at industry, government, and

academic facilities that would enable a basic cost-benefit analysis.[8] Baseless statements about the effectiveness and costs of monitoring the BWC are not only counter to scientific method, they are detrimental to making progress in this important area. The industry experts were taken aback that U.S. negotiators would be at the table for an extended period of time without the benefit of field trial data. In the biopharmaceutical industry, the equivalent would be marketing a drug without clinical or even preclinical trials, but making assertions that the drug might alleviate a condition without negative side effects.

The industry experts concur with the U.S. government that the draft monitoring protocol that Washington rejected in July 2001 was lame,[9] but that does not mean that it cannot be fixed. If the U.S. industry were to abandon the search for a cure for cancer, Alzheimer's, or any other diseases, a public uproar would occur. Yet, the dissolution of the international process to strengthen the BWC has gone virtually without notice.

The U.S. government's stance is all the more puzzling in light of the numerous statements of U.S. policymakers about the gravity of the threat from biological weapons proliferation.[10] The disparity between U.S. rhetoric about the bioweapons threat and U.S. inaction to address it is not simply hypocritical and embarrassing, some would call it irresponsible. Washington is making virtually no effort to create an international compliance inspection mechanism to help reduce the biological weapons threat to U.S. security and international peace. Treaty compliance inspections have served U.S. security interests well in other contexts, most recently, with International Atomic Energy Agency inspections that point to a possible covert Iranian nuclear weapons program.[11]

Granted, the international community has often struggled with the enforcement of treaty prohibitions when noncompliance occurs, but overcoming that problem is a matter of political will and judgment. Inspectors are the international community's eyes and ears, the sentinels that warn of noncompliance. Without them, nations can mount illicit

[8] See the National Security and Corporate Fairness Under the Biological Weapons Convention Act, which became Public Law 106-113, Section 1124, 29 November 1999.

[9] Critiquing the Ad Hoc Group's draft monitoring protocol, the industry experts determined that the protocol deserved a "D." They refrained from giving the draft protocol a failing grade because "Sometimes an 'F' shows a little innovation." *House of Cards: The Pivotal Importance of a Technically Sound BWC Monitoring Protocol*, report no. 37 (Washington, DC: Henry L. Stimson Center, May 2001): 93.

[10] President George W. Bush called biological weapons a "scourge;" Secretary of State Colin Powell said that Iraq's biological weapons were the "greatest concern;" and Under Secretary of State for Arms Control and International Security John Bolton remarked that the threat from biological weapons was "real, growing, and extremely dangerous." George W. Bush, President, "Strengthening the International Regime against Biological Weapons: President's Statement on Biological Weapons" (Washington, DC: 1 November 2001); Colin Powell, secretary of state, "Interview on Fox News Sunday Show with Tony Snow" (Washington, DC: 6 December 2001); John R. Bolton, under secretary for arms control and international security, "Remarks at Tokyo America Center" (Tokyo: 26 August 2002).

[11] "Still Heading for a Showdown: Iran's Nuclear Ambitions," *The Economist* (25 September 2004); Dafna Linzer, "IAEA Orders Iran to Cease Activities," *Washington Post*, 19 September 2004. International Atomic Energy Agency inspectors also brought to light North Korea's violations of the Nuclear Nonproliferation Treaty in 1994. R Jeffrey Smith, "North Korea Broke Nuclear Agreement, Inspectors Conclude: Atomic Energy Agency Condemns `Serious Violation' of Inspection Pact," *Washington Post*, 10 May 1994.

bioweapons programs and the world will be none the wiser, just as was the case with the Soviet and Iraqi bioweapons programs. That prospect alone should be enough to stir the U.S. government to at least explore the feasibility of monitoring the BWC.

Based on their technical acumen and industry experience with inspections, the industry experts believe that inspectors can differentiate between genuine commercial pharmaceutical and biotechnology enterprises and those that are fronting for covert bioweapons programs. After all, one reasoned, "Not even the best criminal can hide everything."[12] In this report, this group of industry experts has charted a reasonable course to begin resuscitating the BWC. If the U.S. government and U.S. industry lack the will even to take the first step, to embark on domestic trial BWC inspections, the future of international bioweapons nonproliferation efforts is grim indeed.

[12] Dr. Claude Nash, 18 June 2004. Dr. Nash, Ph.D. in microbial genetics, is vice president of research and development for the University of Maryland Biotechnology Institute, founded his own biotechnology company, and has over 30 years experience in industry.

Appendix 1
Participant Biographies

William D. Carpenter provided industry perspectives and technical expertise on behalf of the Chemical Manufacturers of America to a variety of domestic and international activities associated with the negotiation of the Chemical Weapons Convention from 1978 to 1994. Dr. Carpenter spent 34 years at Monsanto, retiring in 1992 as vice president and general manager of Monsanto's agricultural technology division. Among many other accomplishments, he developed Roundup and other herbicides. After the Chemical Weapons Convention entered into force in 1997, Dr. Carpenter served as the U.S. representative to the scientific advisory board for the Organization for the Prohibition of Chemical Weapons, the international body that governs the treaty. Dr. Carpenter holds a M.S. and Ph.D. in plant physiology, as well as an honorary D.Sc. from Purdue University.

Kenneth Coleman is a principal scientist at AstraZeneca's Research and Development facility in Boston. As head of the Clinical Microbiology Group, Dr. Coleman is responsible for *in vitro* evaluation of all Research and Development compounds and has served on numerous teams researching the progression of targets and lead chemical series. He is also a member of the Disease Area Team, responsible for creating and enacting business plans for the company. Prior to joining AstraZeneca, he worked for over 25 years at SmithKline Beecham Pharmaceuticals in a variety of positions. His final position with the company was head of the Antimicrobial Profiling and Assay Development Unit, where he was responsible for *in vitro* evaluation of all compounds from development to market. He has authored or co-authored over 25 publications and he holds several patents. Dr. Coleman holds his Ph.D. in microbiology from the University of Nottingham in the United Kingdom.

Ian A. Critchley is the senior director of microbiology at Replidyne, Inc., a specialty pharmaceutical company that is dedicated to the discovery and development of novel antibacterial agents. He is responsible for directing a lab for the evaluation of antimicrobial compounds and oversees the firm's culture collection in support of drug discovery research. He spent the first 10 years of his career with SmithKline Beecham's Pharmaceuticals Research Division in the United Kingdom, where he led the Molecular Pathogenicity Group. In 1996 Dr. Critchley joined the company's Anti-Infectives Research Group in the United States as the group leader and senior investigator of the *In Vitro* Assay Development Group. Prior to joining Replidyne, Dr. Critchley was the director of laboratory services for Focus Technologies' Anti-Infective Services. Dr. Critchley holds his Ph.D. in microbiology from the University of Glasgow, Scotland.

Robert Goldberg retired in 2002 after 15 years at a U.S. pharmaceutical company that ranks in the top 25 on the Fortune 500 list with over $45 billion in sales. His last job with this firm was executive director for strategic and scientific planning. He began his industry career as a technician at a major U.S. pharmaceutical company after receiving a B.S. degree in biology from Villanova. He went on to earn M.A. and Ph.D. degrees in medical microbiology from the Hahnemann School of Medicine at Drexel University,

doing post-doctoral research at the Hershey Medical Center at Pennsylvania State University. Dr. Goldberg spent 11 years at the National Cancer Institute of the National Institutes of Health, working in administration and research related to virology, cell biology, and molecular biology. During that time, he was also a participant in U.S./USSR cancer research exchanges, including some on-site research in the former USSR. Following retirement, Dr. Goldberg has been an independent consultant for a major U.S. pharmaceutical company and has been on the board of directors of the Hepatitis B Foundation.

Dennis M. Gross is an adjunct associate professor of biochemistry and molecular pharmacology at Thomas Jefferson University's College of Medicine and College of Graduate Studies in Philadelphia. He has over 25 years of experience with a leading Fortune 100 U.S. pharmaceutical company in a wide variety of positions, most recently supporting government affairs and policy initiatives at his firm and managing large capital laboratory construction projects in Japan, Italy, Canada, the United Kingdom, and the United States. He has authored or co-authored over 100 scientific papers, book chapters, abstracts and reviews. Dr. Gross received his B.A and M.Sc. in biology from California State University at Northridge and Ph.D. in cell biology from the University of California, Los Angeles and did a postdoctoral fellowship in hematopharmacology at Tulane University School of Medicine in New Orleans. He also lectures at the School of Business and Industry of Florida A&M University in Tallahassee, Florida in the areas of strategic planning and competitive intelligence.

Jennie Hunter-Cevera is president of the University of Maryland Biotechnology Institute, which encompasses the Center for Advanced Research in Biotechnology, the Center for Marine Biotechnology, the Center for Agricultural Biotechnology, the Institute of Human Virology, and the Medical Biotechnology Center. Dr. Hunter-Cevera received her doctoral degree in microbiology from Rutgers University, beginning her industry career at E.R. Squibb in Princeton, New Jersey, as a researcher and later moving to Cetus Corporation. In 1990, she started a consulting company specializing in biotechnology, agricultural and industrial microbiology, bioremediation, and pharmaceuticals. She then went on to direct the Department of Environmental Biology and Biochemistry for the Lawrence Berkeley National Laboratory. There, she started the Center for Environmental Biotechnology, where she remained until becoming president of the University of Maryland Biotechnology Institute in 1999. Dr. Hunter-Cevera has also worked on *Bacillus anthracis* biomarkers, specifically saspB, which is now a classified assay.

Douglas Jaeger retired in 2002 from a U.S. pharmaceutical firm with annual revenues in excess of $15 billion, where over his 35-year career he was an engineer, superintendent, group leader, section manager, and, most recently, the manager of custom fermentation and bioprocessing. In that capacity, Jaeger oversaw project teams and fermentation projects involving a wide variety of microorganisms and processes. Over the years, he worked with numerous microorganisms, including recombinant and conventional cells and non-traditional fermentation microorganisms. He directed the expansion of fermentation and strain improvement operations, including the design and construction of

a state-of-the-art fermentation pilot plant with computer-controlled and monitored fermentors. Jaeger holds a B.S. degree in chemical engineering and an M.S. degree in fermentation biochemistry from the University of Wisconsin. He also holds an MBA from Loyola University, focusing on operations research. He now provides fermentation consulting services as Doug Jaeger and Associates, LLC.

Robert Maigetter joined Immunomedics, Inc., in 2002 as vice president of operations, after eight years in the same capacity at Immune Response Corporation. Between 1975 and 1995, Maigetter held a number of research positions at Merck, becoming the senior manager of biotechnology manufacturing in 1990. Among his many achievements at Merck, he received the Merck Management Council Award for development of PNEUMOVAX®, a vaccine against multiple strains of *Streptococcus pneumoniae*. Before his tenure at Merck, he spent two years as a research microbiologist at the Illinois Institute of Technology Research Institute. Dr. Maigetter received his M.S. and Ph.D. degrees in microbiology at Ohio State University and recently earned a degree in science, engineering, and business from the University of Pennsylvania. He has served on the American Society for Microbiology Biotechnology Task Force and the editorial board of the *Journal of Industrial Microbiology*. Dr. Maigetter is the author of some 35 publications and holds two patents.

Frank J. Malinoski is currently executive vice president and chief medical officer of a U.S. biotechnology company. Previously he was vice president of medical affairs and then of business development for a major U.S. pharmaceutical company with net revenues of over $15 billion in 2003. Dr. Malinoski spent six years of his early career at the U.S. Army's Medical Research Institute of Infectious Diseases (USAMRIID), focusing on vaccine clinical trials and laboratory viral vaccine development. While with USAMRIID, he participated in the first trilateral inspection of the Soviet Union's biological weapons facilities, and also served as an inspector with the United Nations Special Commission in Iraq in 1991. After his tenure with USAMRIID, Dr. Malinoski directed clinical research for Lederle-Praxis Biologicals, focusing on childhood vaccines including pneumococcal, RSV and meningococcal. He later became vice president for medical and clinical affairs for Nabi, and subsequently vice president of clinical affairs for Axis Genetics in the UK. Dr. Malinoski earned his M.D. from Albany Medical College, and Ph.D. in microbiology from Rutgers University.

Claude H. Nash is vice president of the University of Maryland Biotechnology Institute, focused on advanced research in biotechnology, training the future workforce and promoting economic development. Prior to joining the University of Maryland Biotechnology Institute, Dr. Nash was the executive chairman of ViroPharma Incorporated, a biotechnology company he founded in 1994. He has over 30 years of experience in the pharmaceutical industry, working for Eli Lilly & Company, Smith Kline and French laboratories, and Sterling-Winthrop Research Institute. He was previously corporate vice president of Schering-Plough Research Institute, overseeing the tumor biology and infectious disease branch. Over the course of his career he has helped to advance 20 drugs into clinical trials. Dr. Nash holds a Ph.D. in microbial genetics and biochemistry from Colorado State University.

J. Kay Noel runs her own consulting firm, evaluating new technologies and business opportunities for companies in the biotechnology and healthcare industries. Prior to starting her consulting business in 1986, Dr. Noel was vice president of Axion Pharmaceutical's planning and commercial development department. As director of Cetus Corporation's diagnostics business, she founded and managed a business team that developed and marketed ten products in three years. She also developed the first healthcare business plan for Cetus, securing a $75 million R&D partnership to fund the plan. After concluding a National Institutes of Health research fellowship in biophysics at the University of California, Los Angeles, Dr. Noel directed Abbott Laboratories' New Product Research and Development department. Dr. Noel holds a Ph.D. in biophysics from the University of Michigan.

George Pierce became a professor of applied and environmental microbiology at Georgia State University in 2000. Prior to his transition to academia, Pierce worked for nearly 10 years at Cytec Industries, formerly American Cynamid, where his last position was manager of technology development and engineering. He has also held senior research posts with Battelle Memorial Institute and at Celgene Corp., where he was the director of research and development. His research interests include development and scale-up of microbial processes for pollution prevention, site remediation and restoration at Superfund and Resource Conservation and Recovery Act sites, scale-up and development of commercial biotechnology products, development of enzyme based and fermentation based products, and regulatory affairs and compliance in the area of environmental and industrial microbiology. Dr. Pierce holds a Ph.D. in microbiology from Rensselaer Polytechnic Institute, where he was also an adjunct professor.

James Poupard is the president of the Pharma Institute of Philadelphia, a bio-pharmaceutical consulting firm specializing in all aspects of anti-infective life cycle management. Formerly the director of strategic microbiology in the Research and Development division of GlaxoSmithKline, Dr. Poupard has over 40 years experience in the biopharmaceutical industry. During his first 11 years with SmithKline Beecham, he was the group director for clinical microbiology and antimicrobial profiling. At the Medical College of Pennsylvania from 1986 to 1990, Dr. Poupard was the director of clinical microbiology and laboratory medicine/pathology. From 1974 to 1986 he was the director of microbiology and director of laboratory processing at Bryn Mawr Hospital. Among his faculty positions, Dr. Poupard has held professorships in microbiology, pathology, and laboratory medicine at the Medical College of Pennsylvania and Thomas Jefferson University. Dr. Poupard holds an M.S. in clinical microbiology from Thomas Jefferson University and a Ph.D. in the history and philosophy of science from the University of Pennsylvania.

George A. Robertson is vice president for the science and technology division of the PDA, an international association for pharmaceutical science and technology. With over 30 years experience in the biopharmaceutical and biodefense industries, Dr. Robertson's areas of expertise include bioterrorism response and planning, biological safety, new product development, and GMP quality control and validation. As chief scientist with

ITT Industries, he led the design team working on the U.S. Army's Vaccine Pilot Plan, and the team developing biodetectors for the Department of Homeland Security. Dr. Robertson was previously quality control director for Wyeth Vaccines, overseeing the operation of the plant's pharmaceutical chemical, biochemical, *in vivo*, microbiological and environmental testing facilities. As a U.S. Army Reservist, Dr. Robertson served as a biological weapons inspector with the United Nations Special Commission in Iraq, and has served as a biotechnology consultant to the U.S. government. Dr. Robertson holds a Ph.D. in molecular biology from the University of Pennsylvania, and a M.S. in biology from Villanova University.

Appendix 2
U.S. Select Agent Lists

U.S. Select Agent List of Pathogens Dangerous to Humans [1]

note: agents marked with an asterisk (*) are listed as dangerous to both humans and animals

Viruses	Crimean-Congo hemorrhagic fever Eastern equine encephalitis* Ebola Nipah and Hendra Complex* Cercopithecine herpesvirus 1 (Herpes B) Lassa fever Marburg Monkeypox Rift Valley Fever* South American hemorrhagic fever viruses (Junin, Machupo, Sabia, Flexal, Guanarito) Tick-borne encephalitis complex viruses Variola majpr (smallpox) Variola minor (alastrim) Venezuelan equine encephalitis*
Bacteria	*Bacillus anthracis* (anthrax)* *Brucella abortus** *Brucella melitensis** *Brucella suis** *Burkholderia (Pseudomonas) mallei** *Burkholderia (Pseudomonas) pseudomallei** Botulinum neurotoxin producing species of *Clostridium** *Coxiella burnetii** (Q fever) *Francisella tularensis** (tularemia) *Yersinia pestis* (plague)
Rickettsiae	*Rickettsia prowazekii* *Rickettsia rickettsii*
Fungi	*Coccidioides immitis** *Coccidioides posadasii*
Toxins	Abrin Botulinum neurotoxins* *Clostridium perfringens* epsilon toxin* Conotoxins Diacetoxyscirpenol Ricin Saxitoxin Shigatoxin* Shiga-like ribosome inactivating proteins Staphylococcal enterotoxins* Tetrodotoxin T-2 toxin*

[1] Possession, Use, and Transfer of Select Agents and Toxins; Interim Final Rule, Department of Health and Human Services, 42 CFR Part 73, Federal Register 240, no. 67 (13 December 2002): 76898. This list is to be reviewed and updated biennially or more often, as needed. For a comprehensive description of the characteristics of these agents and the medical effects of the diseases they cause, see Frederick R. Sidell, Ernest T. Takafuji, and David R. Franz, eds., *Medical Aspects of Chemical and Biological Warfare* (Bethesda: Office of the Surgeon General, Department of the Army, 1997).

U.S. Select Agent List of Pathogens Dangerous to Animals[2]

note: agents marked with an asterisk (*) are listed as dangerous to both humans and animals

Viruses	African horse sickness African swine fever Akabane Avian influenza Bluetongue Camel pox Classical swine fever Eastern equine encephalitis* Foot and mouth disease Goat pox Japanese encephalitis Lumpy skin disease	Malignant catarrhal fever Menangle Newcastle disease Nipah and Hendra Complex viruses* Peste des petits ruminants Rift valley fever* Rinderpest Sheep pox Swine vesicular disease Vesicular stomatitis Venezuelan equine encephalitis*
Bacteria	*Bacillus anthracis* (anthrax)* *Brucella abortus** *Brucella melitensis** *Brucella suis** *Burkholderia (Pseudomonas) mallei** *Burkholderia (Pseudomonas) pseudomallei** Botulinum neurotoxin producing species of *Clostridium** *Coxiella burnetii** (Q fever) Francisella tularensis* *(tularemia)* *Mycoplasma capricolum/M.*F38/*M. mycoides capri* (contagious caprine pleuropneumonia) Mycoplasma mycoides mycoides *(contagious bovine pleuropneumonia)*	
Rickettsiae	*Cowdria ruminantium* (heartwater)	
Fungi	*Coccidioides immitis**	
Toxins	Botulinum neurotoxins* *Clostridium perfringens* epsilon toxin* Shigatoxin* Staphylococcal enterotoxins* T-2 toxin*	
Other	Bovine spongiform encephalopathy agent (mad cow disease)	

[2]Agricultural Bioterrorism Protection Act of 2002; Possession, Use and Transfer of Biological Agents; Interim Final Rule, Department of Agriculture, Animal and Plant Health Inspection Service, 9 CFR, Part 121, Federal Register 67, no. 240 (13 December 2002): 76932-76933. This list is to be reviewed and updated biennially or more often, as needed.

U.S. Select Agent List of Pathogens Dangerous to Plants[3]

Liberobacter africanus
Liberobacter asiaticus
Peronosclerospora philippinensis
Phakopsora pachyrhizi
Plum pox potyvirus
Ralstonia solanacearum, race 3, biovar 2
Sclerophthora rayssiae var. *zeae*
Synchytrium endobioticum
Xanthomonas oryzae pv. *oryzicola*
Xylella fastidiosa (citrus variegated chlorosis strain)

[3] Agricultural Bioterrorism Protection Act of 2002; Possession, Use and Transfer of Biological Agents; Interim Final Rule, Department of Agriculture, Animal and Plant Health Inspection Service, 7 CFR, Part 331, Federal Register 67, no. 240 (13 December 2002): 76927. The U.S. Department of Agriculture's Animal and Plant Health Inspection Service generated this list based on the Agricultural Bioterrorism Protection Act of 2002. See www.aphis.usda.gov. This list differs considerably from a list proposed by the BWC Ad Hoc Group. See *Ad Hoc Group of the States Parties to the Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on Their Destruction*, 1997, Ad Hoc Group 38/Annex 1, 117. See also Laurence V. Madden and Mark Wheelis, "The Threat of Plant Pathogens as Weapons Against US Crops," *Annual Review of Phytopathology* 41 (September 2003): 155-76.