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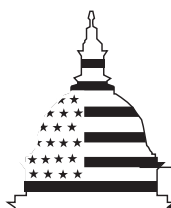
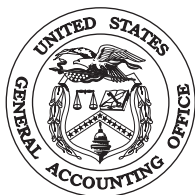
Report to the Chairman and Ranking  
Minority Member, Committee on Armed  
Services, House of Representatives

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July 1999

# DOD ANIMAL RESEARCH

## Controls on Animal Use Are Generally Effective, but Improvements Are Needed



**G A O**

Accountability \* Integrity \* Reliability

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United States General Accounting Office  
Washington, D.C. 20548

National Security and  
International Affairs Division

B-278778.1

July 8, 1999

The Honorable Floyd Spence  
Chairman  
The Honorable Ike Skelton  
Ranking Minority Member  
Committee on Armed Services  
House of Representatives

In 1992 and 1994 the House Committee on Armed Services held hearings on concerns that had been raised by the public and animal welfare interest groups about Department of Defense (DOD) research projects that utilize animals and inadequate public disclosure of DOD's activities involving the use of animals. DOD's Inspector General also investigated DOD's animal use projects and made several recommendations to improve oversight and public accountability. In response to the recommendations, DOD made several changes, including a new and publicly available database of animal use projects,<sup>1</sup> new practices for preparing and reviewing research, and an annual animal use report to Congress.

However, the public and animal welfare groups have continued to raise questions about whether DOD uses animals, particularly higher-order animals such as nonhuman primates, cats, dogs, and farm animals, appropriately. In light of these concerns, your Committee directed us to examine DOD's management and oversight of its animal research programs.<sup>2</sup> As agreed with your offices, we examined to what extent projects funded or performed by DOD utilizing animals (1) were directed toward military objectives; (2) unnecessarily duplicated other research; and (3) incorporated alternatives that reduced, replaced, or refined the use of animals.

We reviewed relevant legislation, regulations, policies, and procedures and interviewed DOD and other federal officials as well as representatives from animal research and animal welfare interest groups. We also reviewed

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<sup>1</sup> In an earlier report we discussed strengths and limitations of the database. See DOD Animal Research: Improvements Needed in Quality of Biomedical Research Database (GAO/NSIAD/HEHS-99-24, Dec. 14, 1998).

<sup>2</sup> House Report 103-499 by the House Armed Services Committee in consideration of the National Defense Authorization Act for Fiscal Year 1995.

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DOD's database of fiscal year 1996 animal use projects, the most current and complete information available at the time of our review, and collected information from various DOD program offices to determine the objectives of each of the projects. We chose 24 of these projects, concentrating on the areas of biological defense, combat casualty care, and radiation research, to examine the issues of unnecessary duplication and the consideration of alternatives.<sup>3</sup> We visited the 14 DOD and other research facilities where these projects were conducted to review applicable processes and records. We also contracted with independent experts to assist our evaluation of these projects. Our findings on the 24 projects are not generalizable to all DOD research that used animals in fiscal year 1996. See appendix I for a detailed discussion of our scope and methodology.

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## Results in Brief

DOD's controls over animal use were generally effective, but some improvements are needed to further ensure that animals are used appropriately. We were able to link all but one of the 805 animal use projects in fiscal year 1996 to a military objective or a congressionally directed program. About half the projects were directed toward military research objectives that evolved from formal DOD planning processes, while about 35 percent supported DOD missions such as medical training and education. Another 15 percent did not address a direct military need but were part of congressionally directed programs such as breast cancer research. Many of the projects that addressed military objectives also had civilian applications such as emergency medicine.

We did not identify any unnecessary duplication in the 24 research projects we reviewed. DOD employed measures to avoid or minimize unnecessary duplication. These measures included requiring investigators to conduct and document literature searches and submit project proposals for scientific and animal use reviews. Although the inherent limitations of any literature search constrain DOD's ability to identify and avoid unnecessary duplication, DOD needs to clarify its requirement that investigators search particular databases of ongoing research to ensure that searches are consistently implemented.

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<sup>3</sup> Our study does not address several other areas where the public and animal welfare groups have raised concerns about DOD's use of animals such as whether the results of animal tests can be extrapolated to humans and whether research on brain injuries should continue to be conducted with animals.

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Although DOD considered and incorporated alternatives to replace and reduce the use of animals in the 24 research projects we reviewed, investigators could have used additional alternatives to refine experimental procedures in 8 of them. These refinements could have improved the welfare of the animals without compromising the projects' objectives. For example, routine pain relief could have been administered in five studies of burn treatments. In two other studies, animals could have been euthanized earlier than the investigators proposed without affecting research results. However, we were unable to determine the extent to which refinement alternatives were considered in the development and review of these protocols because records did not document the alternatives that were considered and not adopted.

We are making recommendations to the Secretary of Defense intended to reduce the likelihood that proposed research unnecessarily duplicates other research and to improve the consideration of refinement alternatives.

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## Background

In fiscal year 1996, DOD sponsored 805 projects using a total of 319,000 animals.<sup>4</sup> These projects were conducted at various DOD research and training facilities (such as the U.S. Army Medical Research Institute for Infectious Diseases) as well as at public and private research facilities (such as universities and hospitals) funded by DOD. The animals used ranged from fish and amphibians to farm animals and nonhuman primates. However, mice and rats accounted for 80 percent of the animals used.<sup>5</sup> These projects encompassed a very diverse set of research, training, and education activities. For example, in several projects, DOD tested different vaccines and treatments on various species of monkeys that were exposed to biological warfare agents or infectious diseases. Other projects used sheep, pigs, rats, and rabbits to investigate burn treatment therapies. Some projects used rhesus monkeys, dogs, guinea pigs, ferrets, and rodents to assess the health effects of ionizing radiation. Furthermore, as part of their training in emergency medicine, military surgeons and medics performed practice surgeries on pigs, goats, and other animals.

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<sup>4</sup> DOD was unable to provide us with an estimate of the total cost of these projects but did provide an estimate for its animal use projects for fiscal year 1997, amounting to about \$100 million.

<sup>5</sup> DOD summarized the data in [Department of Defense Animal Care and Use Programs 1996: Report to the Senate Armed Services Committee and the House of Representatives National Security Committee](#).

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DOD is subject to federal laws and regulations governing how animals are used as subjects in research and training projects. These laws and regulations establish standards for the care and use of animals in research and training, including requirements to minimize the potential for unnecessary duplication and promote the use of alternatives.<sup>6</sup> In addition, DOD has established its own policies and guidelines governing animal use. DOD officials and other experts generally agree that unnecessary duplication, although not formally defined by law or regulation, refers to research that repeats existing procedures without contributing to the advancement of scientific knowledge or presenting new information. Some duplication is usually necessary because research results must be reproducible. Reproduction is achieved when investigators replicate prior research to determine whether similar results do occur. DOD and other experts view alternatives as methods (such as computer simulation and cell culture techniques) that replace or reduce the number of laboratory animals required for an investigation or refine an existing procedure to minimize an animal's pain or distress.

Overall responsibility for establishing policies on animal use activities within DOD resides with the Director of Defense Research and Engineering, while implementation of the policies resides with each armed service or Defense agency such as the Armed Forces Radiobiology Research Institute. The principal agent for ensuring that regulations and policies are implemented at DOD and non-DOD facilities rests with institutional animal care and use committees (IACUC). DOD's policy is that its IACUCs have a minimum of five members, including at least one doctor of veterinary medicine and at least one member not affiliated with the institution in any other way.

DOD's process to reduce unnecessary duplication and promote alternatives relies upon investigators to prepare detailed plans—called protocols—of their proposed animal use activities and several levels of review of these protocols. DOD's policy states that protocols must contain descriptions of the research or training activity, justifications for the use of the animals, descriptions of the experimental procedures, steps to be taken to protect the welfare of the animals, and the results of literature searches carried out to detect unnecessary duplication and availability of alternatives. These items are included in DOD's standard protocol format, which was adopted

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<sup>6</sup> The Animal Welfare Act, 7 U.S.C. 2131-2158, as amended which is implemented by USDA regulations 9 C.F.R. Parts 1-4; and the Health Research Extension Act of 1985, 42 U.S.C. 289d.

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for fiscal year 1996. Before investigators can begin using animals, the DOD funding agency reviews their protocols for scientific merit, and the IACUC reviews them for animal care considerations. As part of their review, IACUCs assess whether available alternatives were considered and adopted where appropriate. In addition, DOD requires that a service-level veterinarian review all its projects at non-DOD facilities as well as projects at DOD facilities using nonhuman primates. See appendix II for a detailed discussion of DOD's process for reviewing animal use projects.

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## DOD Animal Use Projects Generally Addressed Military Objectives or Congressional Directives

We were able to link all but one of the 805 animal use projects in fiscal year 1996 to military objectives or congressionally directed programs. Projects addressing military objectives included a variety of research, training, and education activities, while those addressing congressionally directed programs were primarily outside DOD's military mission in areas such as breast cancer research. Many of the animal use projects directed at military objectives also addressed civilian needs.

We attempted to collect information on the objectives of DOD's animal use projects from its fiscal year 1996 Biomedical Research Database (BRD), a central source of information on the 805 projects conducted that year. While it contained information on the location of the research and a brief statement of the projects' research objectives and methods, the database lacked information on the link between the projects and specific military or congressional objectives.<sup>7</sup> As a result, we had to contact 16 different DOD program offices, including the U.S. Army Medical Research and Materiel Command, the Office of Naval Research, the Air Force Office of Scientific Research, and the Armed Forces Radiobiology Research Institute (AFRRI), to obtain information on objectives.

The individual program offices varied in how they were able to identify objectives for the projects. Officials in some offices were able to do so using documentation in existing records. In other offices, however, DOD lacked documentation, but program officials used their knowledge of the work to link each project. We were able to link 688 of the 805 projects to military objectives and another 116 to congressionally directed programs that did not have direct military relevance (see table 1).

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<sup>7</sup> In December 1998 we recommended that DOD more clearly link projects with research goals and justifications in the BRD. See [DOD Animal Research](#) (GAO/NSIAD/HEHS-99-24, Dec. 14, 1998).

**Table 1: DOD Animal Use Objectives (fiscal year 1996)**

Objectives	Number of projects
Objectives developed within a formal research planning process to support military objectives	
Combat casualty care	87
Infectious diseases	70
Biological weapons defense	67
Operational medicine	57
Toxicity studies and environmental assessments	43
Medical chemical defense	30
Sensor development	16
Assessing effects of naval activities on marine mammals	14
Medical radiological defense	4
<b>Subtotal</b>	<b>388</b>
Objectives that supported other military needs	
Clinical investigations	146
Training	82
Toxicity evaluations	31
Other mission objectives	41
<b>Subtotal</b>	<b>300</b>
Objectives that supported congressionally directed programs	
Breast cancer research	98
Pathology research	17
Neurotransmitter research	1
<b>Subtotal</b>	<b>116</b>
Objectives not linked to military needs or congressionally directed programs	1
<b>Total</b>	<b>805</b>

Of the 688 projects that we found linked to military objectives, 388 addressed specific military research objectives identified through DOD's formal research planning processes. These 388 projects used most of the animals as well as most of the nonhuman primates.

The projects' objectives evolved from processes that DOD and each of the services established to identify operational military requirements and develop appropriate research to address these requirements. Each year, DOD's Director of Defense Research and Engineering develops formal



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programming guidance for each of the services to help ensure that their research efforts support the current and long-term needs of the Department. This guidance is provided primarily in three plans: the Basic Research Plan, the Defense Technology Area Plan, and the Joint Warfighting Science and Technology Plan, which identify objectives and investment strategies for technologies critical to DOD's missions. Each service has its own planning and review process to address the objectives identified in the plans and to develop other objectives and strategies to meet its own research needs. The services collect input from other DOD components that are the principal users of the research results and match their own needs with existing budget resources and research capabilities. The services then develop and publish specific annual research plans. Various programs conduct individual research projects to support these specified research objectives.

The projects that were linked to research objectives developed within DOD's formal research planning process were designed to improve the readiness and capabilities of servicemembers by developing information, products, and technologies. For example, the infectious disease projects used nonhuman primates and other animals to develop vaccines to protect servicemembers from infectious diseases such as malaria, dengue fever, hepatitis, and typhus. The operational medicine objective included projects using rats and other animals to develop countermeasures against the effects of operational stress (such as sleep deprivation and fatigue) on military performance. The sensor development projects used marine mammals and other animals to develop information to improve the military's ability to detect underwater and airborne objects.

The projects that supported other military objectives did not focus on meeting DOD's operational research requirements. Instead, they supported other mission-related activities such as medical education and training. For example, faculty, students, and physicians at DOD medical treatment and training centers conducted clinical investigations to improve the knowledge and skills of medical professionals. One clinical investigation project used hamsters to determine the effect of high-pressure oxygen on tumors of the mouth. The training projects were intended to develop the skills of medics, corpsmen, and other military medical personnel. For example, cats and ferrets were used in several military hospitals in the training of physicians in inserting tracheal tubes into pediatric patients. The toxicity testing projects used different animals to evaluate the health hazards of various munitions and compounds found on military bases.

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The projects conducted as part of congressionally directed research programs did not address direct military objectives. Most of them were part of the congressionally directed Breast Cancer Research Program, administered by the Army. These projects investigated a wide range of concerns about breast cancer, including molecular biology, detection, diagnosis, and treatment. The pathology projects were conducted at the Armed Forces Institute of Pathology as part of a congressionally directed research program in which DOD pathologists collaborate with civilian pathologists.

We were unable to link one project with a military need or a congressionally directed program. In this project, a private corporation conducted anemia research on rabbits in a Navy laboratory overseas. DOD officials agreed with our assessment that this project, which has ended, did not address a military need or a congressionally directed program.

We found that some of the projects that addressed military objectives also had civilian applications because the medical needs of military personnel are often similar to those of the civilian population. In particular, projects addressing combat casualty care and infectious diseases for military personnel have direct relevance to the treatment and care of civilians. For example, as part of its combat casualty care program, the Army used pigs and rabbits to develop and test a fibrin bandage containing plasma proteins that accelerate blood clotting. The Army is currently collaborating with the American Red Cross to commercialize this technology for uses in both the military and civilian sectors. Similarly, DOD used nonhuman primates and other animals to develop vaccines against hepatitis, malaria, dengue virus, and other infectious diseases that affect military and civilian populations.

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## **DOD Efforts to Avoid Unnecessary Duplication Generally Succeeded**

We did not identify any cases of unnecessary duplication in our review of 24 DOD-funded research projects that used animals in fiscal year 1996. DOD, research facilities, and investigators employed several measures to minimize the risk of duplicating other studies unnecessarily. Nonetheless, certain factors such as the limited effectiveness of literature searches could affect DOD's ability to systematically identify and avoid unnecessary duplication.

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**No Evidence of Unnecessary Duplication in 24 Projects**

We identified no unnecessary duplication in the 24 research projects conducted in fiscal year 1996 that we reviewed. We evaluated each project in several ways. We reviewed the materials used in the original consideration and approval of the project and interviewed principal investigators and IACUC members to determine how they addressed the likelihood that the project would unnecessarily duplicate other studies. We provided the same materials to the U.S. Department of Agriculture's Animal Welfare Information Center (AWIC) and had its information specialists conduct an independent search of scientific literature relevant to each project.<sup>8</sup> We then had a nationally recognized subject matter expert and two experts in research methodology and animal use alternatives separately review the materials and the AWIC literature search for each project.

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**Practices Used to Help Avoid Unnecessary Duplication**

Each of the 14 facilities we visited had practices in place to help ensure that investigators' research did not unnecessarily duplicate other studies. Investigators conducted searches of published literature in their fields. The literature searches varied in the number and types of databases used. However, as recommended by DOD, investigators generally searched major databases such as MEDLINE.<sup>9</sup> Investigators of the 24 research protocols provided written assurance, as required, that they had made a good faith effort to ensure that their project would not unnecessarily duplicate other research.

Investigators we spoke with also mentioned other practices they employed to reduce the likelihood of unnecessary duplication. They emphasized that attending seminars and conferences in their particular subject area, consulting and collaborating with other experts, and reviewing relevant professional publications all contributed to their ability to stay current in their field. Investigators further noted that the desire to publish results of their findings in peer-reviewed journals provided additional incentive for avoiding unnecessary duplication because journals seek to publish research that could advance science. All but four of the projects we

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<sup>8</sup> AWIC, an information service of the National Agricultural Library, was established to provide technical assistance in conducting searches to identify alternatives.

<sup>9</sup> MEDLINE is the National Library of Medicine's bibliographic database covering the fields of medicine, nursing, dentistry, veterinary medicine, health care systems, and other sciences. The MEDLINE file contains bibliographic citations and author abstracts from approximately 3,900 biomedical journals published in the United States and 70 other countries.

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reviewed resulted in one or more peer-reviewed publications and/or conference presentations.

The 24 research projects also went through several reviews that partly addressed the potential for unnecessary duplication. For example, all but one project went through a scientific merit review. According to DOD guidance, such reviews include a consideration of the project's contribution to science. Scientists and department heads located at DOD's research facilities conducted scientific merit reviews for 16 of the 17 sampled projects at those facilities. As for the remaining project, an agency official told us that a science review was not required at the time the project was approved. The seven projects at the non-DOD facilities we visited went through either a peer review by non-DOD scientists or a review by a DOD scientist from the program funding office.

Each project was also reviewed by the IACUC at its research facility. Some of the IACUC chairpersons stated they reviewed the investigators' written assurance statements and literature search documentation. The IACUCs relied on investigators to review abstracts and articles obtained from literature searches, and identify unnecessarily duplicative research. However, the IACUCs generally did not independently replicate the literature searches. Some of the IACUCs used other resources to assist them in their review. For example, the IACUC at one DOD facility required investigators to work with a reference librarian to perform literature searches and submit the search results for IACUC review. At two DOD and one non-DOD facility, a reference librarian served as an IACUC member to focus on the quality and appropriateness of the investigators' literature searches.

DOD also requires that a service-level veterinarian trained or experienced in laboratory animal science and medicine perform a review of all projects at non-DOD facilities as well as projects involving the use of nonhuman primates. The purpose of these reviews is to ensure that the research projects adhere to DOD's policies and requirements. DOD, however, did not always enforce its requirement for these service-level veterinarian reviews. We found that one Defense Advanced Research Projects Agency (DARPA) and two AFRRRI projects did not receive the required service-level veterinary reviews because no veterinarian was assigned to them. For the DARPA project, a service-level veterinarian was not assigned to review the protocol until approximately 1 year after the project began. The two AFRRRI projects were completed without ever receiving such a review. When we pointed out this problem to AFRRRI officials, they made

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arrangements to have a service-level veterinarian perform the required reviews on all their ongoing projects that use nonhuman primates.

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## Two Factors Could Limit the Effectiveness of Literature Searches

Although DOD relies on literature searches as a key element to reduce the likelihood that proposed research would duplicate other work unnecessarily, two factors could limit the searches' effectiveness. First, the services and Defense agencies that sponsor research at non-DOD facilities differed in their implementation of a key aspect of literature search requirements. Second, literature searches are limited in their ability to identify potentially duplicative research because not all research is published.

Since 1995, DOD has required that all investigators search the Defense Technical Information Center (DTIC) and the Federal Research in Progress (FEDRIP) databases or their equivalents. Searching these databases is important because they are the primary sources of information on research in progress in the federal government. We previously reported that it is important that investigators have access to such information because of the time lag between completing research and publishing.<sup>10</sup>

We found, however, that the policy on searching these databases of ongoing research or their equivalents is not clear. In particular, service-level veterinarians differed in their interpretation of the meaning of equivalent. For example, the veterinarian who reviewed DARPA projects told us that he does not recognize any other databases in lieu of DTIC and FEDRIP. However, the Army's veterinarian considers MEDLINE to be the equivalent of FEDRIP. In contrast, the Navy's veterinarian told us that he does not accept MEDLINE as an equivalent to FEDRIP but does accept a search of the National Technical Information Service database.<sup>11</sup>

Although DOD officials, principal investigators, and experts emphasized the importance of conducting literature searches, they also noted that literature searches have inherent limitations in identifying unnecessary duplication. These limitations affect all research, whether funded by DOD

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<sup>10</sup> Biological Warfare: Better Controls in DOD's Research Could Prevent Unneeded Expenditures (GAO/NSIAD-91-68, Dec. 27, 1990).

<sup>11</sup> The National Technical Information Service is the government's central source for the sale of scientific, technical, engineering, and related business information produced by or for the U.S. government.

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or by other public or private organizations. For example, studies that show no effect are not generally published. In addition, some research involves proprietary information and rarely gets published; other research involves classified information and never gets published. Because of all the research that is not published, investigators may not be able to identify the full extent of research that has been conducted in their field.

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## DOD Could Do More to Promote the Use of Alternatives

Although DOD's efforts to promote alternatives in animal research have generally been successful in the replacement or reduction of the animals used, we found additional refinements that could have been implemented to reduce animals' pain or distress in 8 of the 24 protocols. We found two additional projects in which investigators and IACUCs could have more closely addressed alternatives after investigators proposed changes to previously approved protocols. Identifying and implementing alternatives is challenging, but investigators did not adequately document the alternatives that were considered when they designed their studies.

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## Protocols Addressed Replacement and Reduction Alternatives

In the 24 protocols we reviewed, investigators addressed replacement and reduction issues as required by explaining why they planned to use animals and the proposed species and numbers of animals. To assess DOD's use of alternatives, we reviewed materials used in the original consideration and approval of the project and had a nationally recognized subject matter expert and two experts in research methodology and animal use alternatives separately review the materials for each project. In all 24 protocols, investigators provided explanations of why they planned to use animals to meet research objectives. In 18 of the 24 protocols, investigators provided detailed discussions of the reasons for using animals, including reasons why proposed research could not be done using nonanimal models such as cell cultures or computer models. For example, the investigator on a study of a new type of skin graft justified the use of animals by explaining that cell cultures could not be used to determine the success of these grafts in treating burns and that animals were needed to assess the immune system's response to the grafts. Documenting the consideration of replacement alternatives became a requirement when DOD adopted its standard protocol in fiscal year 1996. This documentation is intended to assist reviewers' ability to determine the quality of investigators' consideration of replacement alternatives.

In two protocols, investigators identified and incorporated nonanimal models as ways to reduce, though not totally replace, animal use. For

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example, in one protocol, the investigator proposed to use cell cultures to screen vaccines before they were tested on mice. This process was designed to reduce the number of vaccines used on the mice, thus reducing the number of mice required.

Investigators' explanations for the proposed use of a specific animal species usually focused on why the species was most appropriate to meet research objectives. The specificity with which protocols addressed this issue varied widely, reflecting differences in facilities' protocol forms. For example, justifications ranged from check marks on a standard checklist of reasons why the animals might be used to detailed discussions of the advantages of using the requested species. One protocol we reviewed contained a detailed discussion of why monkeys and dogs were the best species for the proposed experiments and why rodents, as an alternative lower-order species, were not as well-suited. This discussion was supported by an extensive bibliography. In addition, four of the six biological warfare defense protocols we reviewed proposed using monkeys and provided written justification explaining that a monkey's response to biological warfare agents is similar to a human's. Similarly, the use of pigs in several research protocols exploring resuscitation treatments was proposed because pigs have a cardiovascular system similar to that of humans.

The protocols we reviewed also showed consideration of the number of animals being proposed for use in the research. We found cases in which investigators incorporated methods to reduce the number of animals. In one protocol, the investigator planned to use historical data from previous experiments rather than using additional animals as a basis for comparison. In another protocol, the investigator designed the study to use one animal control group with two experimental groups of animals instead of a separate control group for each experimental group. In a third protocol, the investigator planned to use an alternative statistical technique that would reduce the number of animals needed while still achieving statistically valid results. In addition, since fiscal year 1996, investigators at DOD facilities have been required to certify that statisticians have reviewed proposed research to help ensure that the lowest number of animals as possible is used consistent with research objectives. Investigators at non-DOD facilities are required to provide similar information in their proposals to DOD.

We found one project in which the number of animals could have been reduced, had the investigator reversed the sequence of proposed animal

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procedures. In this case, the investigator planned to first measure the accuracy of an ingestible device in detecting the onset of traumatic shock in pigs. He then planned to assess how long the device would remain effective in the digestive systems of monkeys, whose digestive system is similar to humans'. The investigator planned to wound the pigs but not the monkeys. The investigator requested and received approval to test 400 pigs but not the monkeys. We believe that the monkeys should have been tested first because had the device not remained effective in the monkeys' digestive systems, experiments on the pigs would not have been necessary. However, DOD subsequently terminated funding for this project due to budget reductions, and the second component involving the monkeys was never conducted. A service-level veterinarian agreed with us that it would have been preferable to have first tested the monkeys.

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### Protocols Addressed Refinements but More Could Have Been Done

All the protocols we reviewed described refinements to be used as required to alleviate pain. However, we found that other refinement alternatives were available and could have been used in 8 of the 24 protocols. We were unable to determine the extent to which these refinements were considered because documentation was generally lacking.

All the protocols we reviewed described procedures for administering pain relief to animals as required and euthanizing them when appropriate. In addition, the investigator of one project on experimental burn treatments identified alternative anesthetics and analgesics to be used to improve pain relief for animals. In another case, the IACUC required that the investigator reduce animals' pain and distress by euthanizing them earlier than the investigator had proposed. In this study of burn treatments, the IACUC required the investigator to euthanize rats when their body temperature dropped 4 degrees because scientific literature had demonstrated that such a temperature drop indicates impending death. The investigator had not proposed euthanizing the rats until later. Subsequent to approval of the protocol for this research, the IACUC issued a written policy requiring investigators to consider this alternative when preparing protocols.

In contrast, we found that other refinement alternatives were available and could have been used in 8 of the 24 protocols. In five of these, the alternative was a refinement in the administration of pain relief to animals subjected to burns. In these protocols, sheep, pigs, rats, and mice were to be anesthetized while third-degree burns were being administered. However, the investigators did not plan to give the animals analgesia routinely after the burns. Investigators or attending veterinarians were to



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monitor animals for behavioral changes usually associated with pain or distress such as postural changes, ruffled hair coat, and lack of appetite before administering analgesia. DOD officials stated that in general, pain relief was not needed after the burns were administered because the burns were limited to a well-defined area where the nerve endings had been destroyed by the burns, resulting in no pain.

Whether analgesia should be administered on a routine or as-needed basis in these situations is controversial. Experts and non-DOD officials involved in regulating animal research told us that in experiments such as these, animals can experience pain around the periphery of the burned area and should be given analgesia routinely after burns are administered. They also pointed out that it can be difficult to identify pain in animals and that if the results of the research would not be compromised, routine administration of analgesia is warranted as a preventive measure. DOD officials acknowledged that there is uncertainty over the issue.

Given this controversy, we believe that investigators and IACUCs should fully consider the appropriateness of analgesia administration in similar studies. Neither the investigators' protocols nor the IACUC records, however, contained information on whether refinements involving the routine administration of analgesia had been considered. For example, at a non-DOD facility where one of these five studies was conducted, the IACUC record of consideration consisted only of the protocol number, which was listed among over two dozen protocols approved at one meeting, and brief notes on additional information requested by the IACUC. None of the requested information concerned the use of analgesia. Similarly, at another facility we visited, the Association for Assessment and Accreditation of Laboratory Animal Care International, an independent accreditation organization,<sup>12</sup> found that the IACUC did not adequately document that pain and distress were addressed in the protocol approval process. DOD's standard protocol format, which was implemented in fiscal year 1996, does not require investigators to discuss refinement alternatives that are considered but not adopted.

Other refinement alternatives could have been implemented in the sixth and seventh projects. In these projects, mice that had been given a toxin could have been euthanized sooner, on the basis of a drop in their body temperature, without compromising the research results. The presence of

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<sup>12</sup> DOD requires that all of its facilities apply for AAALAC accreditation.

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hypothermia (low body temperature) as an objective indicator of impending mortality for this type of toxin was published as early as 1992, before the development of both protocols.<sup>13</sup> Although evidence of the effectiveness of this measurement approach was available and was employed in one of the other protocols we reviewed, DOD officials said that the validity of the evidence had not yet been demonstrated on different types of research and species of animals. Researchers at Army laboratories recently conducted two studies to investigate the hypothermia-based end-point indicator. While one of the studies confirmed a correlation between lowered body temperature and mortality, the other was unable to identify a similar correlation. None of the records we reviewed contained information on investigators' or IACUCs' consideration of this refinement.

In the eighth protocol, an alternative vaccine could have been used in a study testing the effectiveness of a vaccine to protect monkeys from a potential biological warfare agent. In this study, monkeys that had been treated with an experimental vaccine against staphylococcal enterotoxin B were exposed to the toxin. The vaccine was prepared from the toxin and, as a result, had a greater likelihood of having side effects that could cause pain and distress to the monkeys than a vaccine prepared using a recombinant technique. Research had been published as early as 3 years before this protocol was prepared pointing to the availability of recombinant techniques for developing a vaccine against this toxin.<sup>14</sup> However, the protocol and IACUC records did not address this alternative.

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## Identifying Alternatives Is Challenging

Finding alternatives that can be used in research is challenging for investigators. These challenges affect all research, whether it is funded by DOD or by other public or private organizations. Although DOD requires investigators to conduct a literature search to identify alternatives to painful procedures, literature searches may not capture all the possible alternatives, in part because the literature may not specifically identify alternatives. For example, an investigator may have used an innovative type of anesthesia on animals but may not have discussed the procedure in the published results of the research. Because alternatives cut across

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<sup>13</sup> Soothill, J.S., Morton, D.B., and Ahmad, A., "The  $HID_{50}$  (hypothermia-inducing dose 50): an alternative to the  $LD_{50}$  for measurement of bacterial virulence," International Journal of Experimental Pathology (Feb. 1992), pp. 95-98.

<sup>14</sup> Harris, T.O., et al., "Lack of complete correlation between emetic and T-cell-stimulatory activities of staphylococcal enterotoxins," Infection and Immunity (Aug. 1993), pp. 3175-3183.

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many fields of research, investigators need to search numerous sources, including some abroad, to find available information on alternatives.

The universe of alternatives is broad and changes constantly. An alternative can be as narrow as a better form of anesthesia and as broad as cell cultures and computer models which do not use animals at all. At the same time, scientific advances can lead to the development of new alternatives. One example is the development of nonanimal procedures for the production of monoclonal antibodies. Previously, these antibodies were produced primarily using animals such as mice but they can now be produced using cell culture techniques.

AWIC and the Center for Alternatives to Animal Testing<sup>15</sup> are working on projects, supported by the Office for Protection from Research Risks (OPRR) of the National Institutes of Health, designed to help improve the usefulness of literature searches for alternatives by making it easier to find alternatives among the numerous online sources. OPRR has entered into an agreement with AWIC to develop an interactive Internet-based training program on searching for alternatives. The program will be based on AWIC's existing training program on literature searching for alternatives. Also, OPRR has been working with the Center for Alternatives to Animal Testing to explore the development of a comprehensive search engine for the numerous electronic sources of information on alternatives. These efforts could assist all researchers, including DOD-funded investigators, to more effectively and efficiently identify alternatives.

In addition, continuing review of protocols at some facilities could be more rigorous. While the facilities we visited generally had procedures in place to ensure that IACUCs reviewed and approved significant changes to protocols after research had begun and conducted periodic reviews of investigators' progress in completing their protocols, we found instances in which investigators and IACUCs could have more closely addressed alternatives. One protocol at a non-DOD facility underwent numerous major changes after it was originally approved by the institution's IACUC. The scope of the project was expanded to inflict injuries on different parts of pigs' bodies, change pain killers used on the pigs, and assess different resuscitation treatments on the pigs. We found no evidence in the amended

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<sup>15</sup> This center, based at Johns Hopkins University in Baltimore, Maryland, operates the ALTWEB Internet site, which provides links to numerous sources of information on animal use alternatives.

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protocols or IACUC records we obtained that alternative procedures were considered.

In an experiment at a DOD facility to develop field techniques for resuscitating severely injured servicemembers, the first 14 of 21 pigs (67 percent) that were tested died unexpectedly. Because it was concerned about the high ratio of deaths, the IACUC considered and approved changes intended to reduce the risk of death from the surgical procedures. But in a later phase of the experiment, 11 of 28 pigs (39 percent) died, in part because of the inexperience of a project member who performed the surgical procedures. In a memo explaining these deaths to the facility's IACUC, the investigator set the goal of reducing the mortality rate in this experiment to not more than 20 percent. The investigator put in place provisions (such as additional training for surgical staff) intended to correct the problems that caused these deaths. Although we found evidence that the IACUC was responsive to the unexpected deaths, which occurred over a period of several years, it acted only after a high number of deaths had occurred. However, the IACUC subsequently implemented a policy requiring investigators to report any unexpected deaths within 48 hours.

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## Conclusions

DOD's controls on animal use were generally effective but improvements are needed. Although we were able to link virtually all animal use projects to military objectives, DOD lacks centralized information on the military justification for each project. Without such information, neither Congress nor the public have an adequate basis for understanding and assessing the reasons DOD uses animals in its research. We continue to believe that DOD should implement our previous recommendation to improve the information reported on individual projects that use animals.

DOD implemented several procedures that worked well to avoid unnecessary duplication by the 24 projects we reviewed. We did not find unnecessary duplication by any of these projects. However, the process for assessing duplication could be improved further. DOD has not adequately defined what it considers appropriate databases for literature searches. We are concerned that as a result, investigators at non-DOD facilities may not routinely search databases such as FEDRIP and DTIC that provide information on government research in progress. Information on ongoing research is important to help investigators identify the potential for unnecessary duplication.

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DOD was generally successful in considering and implementing replacement and reduction alternatives in the 24 research projects we reviewed. However, we found additional refinements that could have been implemented in one-third of these projects. We recognize the challenges that investigators and IACUC members face in identifying alternatives, especially because scientific literature does not always discuss alternatives and scientific and veterinary practices change rapidly. Furthermore, uncertainty remains over the need to use some alternatives such as the routine administration of analgesia in burn studies. However, we were unable to determine the extent to which the refinements we identified were considered by investigators and IACUCs because protocols and IACUC records did not document the alternatives that were considered but not adopted. DOD has adopted a standard protocol requiring investigators to discuss replacement alternatives considered but not adopted. A similar requirement to document the refinement alternatives that were considered could encourage investigators to focus more on these alternatives and provide IACUCs better information on alternatives when they review protocols.

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## Recommendations

To further reduce the likelihood of proposed research unnecessarily duplicating other research, we recommend that the Secretary of Defense clarify DOD's policy regarding which databases of research in progress investigators must search. We also recommend that the Secretary further facilitate the consideration of refinement alternatives by investigators and IACUCs. Specifically, the DOD standard animal use protocol form should be amended to require investigators to identify refinement alternatives that were considered but not adopted and explain why they were not adopted.

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## Agency Comments

In written comments on a draft of this report (see app. III), DOD concurred with our recommendations. DOD stated that it will clarify the databases that should be searched for research in progress and will amend the standard protocol to identify refinement alternatives that were considered but not adopted and to explain why specific alternatives were not adopted.

DOD raised a concern about the title of the report, saying it should be changed by replacing the word "needed" with "suggested." DOD believed that the term "needed" implies that improvements are required or necessary to meet a standard, and noted that our report did not present instances in which federal standards were not met. While we found no

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evidence that DOD failed to meet federal standards, the changes we are recommending are necessary to guard against unnecessary duplication and to promote the implementation of alternatives in DOD's projects that utilize animals. DOD also included technical comments in its response which we incorporated where appropriate.

We are sending this report to the Honorable William Cohen, Secretary of Defense and other interested parties. We will also make copies available to others upon request.

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If you have any questions about this report, please call Kwai-Cheung Chan at (202) 512-3092 or Stephen P. Backhus at (202) 512-7101. GAO contacts and staff acknowledgements are listed in appendix IV.



Kwai-Cheung Chan  
Director, Special Studies and Evaluations  
National Security and International Affairs Division



Stephen P. Backhus  
Director, Veterans' Affairs and Military Health Care Issues  
Health, Education, and Human Services Division



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**Abbreviations**

AFRRI	Armed Forces Radiobiology Research Institute
AWIC	Animal Welfare Information Center
BRD	Biomedical Research Database
DARPA	Defense Advanced Research Projects Agency
DOD	Department of Defense
DTIC	Defense Technical Information Center
FEDRIP	Federal Research in Progress
IACUC	Institutional Animal Care and Use Committee
OPRR	Office for Protection from Research Risks

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# Scope and Methodology

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Our objectives were to determine to what extent projects using animals funded or performed by the Department of Defense (DOD) (1) were directed toward military objectives; (2) unnecessarily duplicated other research; and (3) incorporated alternatives that reduced, replaced, or refined the use of animals.

To assess the extent to which animal use projects were directed toward military objectives, we used the Biomedical Research Database (BRD) to identify the universe of projects using animals being conducted by DOD. We used the fiscal year 1996 BRD because it contained the most current summary information on animals used in research, education, training, and testing at the time we began our review.<sup>1</sup> This database covered 805 animal use projects conducted by DOD and the military services.

Because the BRD does not include information about military objectives for each project, we collected this information from the 16 DOD program offices that sponsor animal use projects. We asked officials there to identify the specific service-level research objectives linked to each project. We reviewed documentation, where available, to confirm their assessments. For other projects, we relied on officials' assessments, which were based on their knowledge of the projects that had been conducted. We also interviewed DOD officials in 14 offices that have responsibility for developing military research objectives and policies for clinical investigations and reviewed policies and reports.

To address our second and third objectives, we reviewed legislation and regulations related to the welfare of research animals and relevant DOD policy documents and directives. We reviewed published literature on animal use issues and attended conferences on this subject. We interviewed veterinarians and others who manage DOD's laboratory animal use programs. We also met with representatives from government agencies, accrediting organizations, animal welfare groups, and others, including the:

Animal Plant and Health Inspection Service, United States Department of Agriculture (USDA);

Animal Welfare Information Center, USDA;

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<sup>1</sup> The BRD does not include information on DOD's use of animals for human or animal consumption, ceremonial activities, and recreation or its training, care, and use of military working animals.

National Institute of Environmental Health Sciences, National Institutes of Health (NIH), Department of Health and Human Services (DHHS);

Office for Protection from Research Risks, NIH, DHHS;

American College of Laboratory Animal Medicine;

Association for Assessment and Accreditation of Laboratory Animal Care International;

Humane Society of the United States;

In Defense of Animals;

Physicians Committee for Responsible Medicine;

Center for Alternatives to Animal Testing, Johns Hopkins University;

National Association for Biomedical Research; and

Institute of Laboratory Animal Research, National Academy of Sciences.

To review research projects, we selected projects from three areas of DOD research: treatment of injuries from biological weapons, combat casualty care, and treatment of radiation wounds. These three areas included 175 of the 805 fiscal year 1996 projects. They are areas of research in which animals are often injured or exposed to potentially deadly agents and in which the animals often either die of their wounds or are euthanized at the conclusion of the study. These areas also included a large proportion of projects that used higher-order animals such as nonhuman primates. We did not review projects in other areas where animals are used such as infectious diseases, chemical defense, human systems technology, and training and education.

From the 175 projects in the three areas we selected, we judgmentally selected 24 projects to review in depth. We selected projects that used large numbers of animals. In selecting specific projects, we also tried to include a wide range of species of animals, a mixture of DOD and non-DOD facilities, and several military services and Defense agencies. Seven of the 24 projects used nonhuman primates and 12 used pigs, dogs, sheep, or rabbits. The other projects used large numbers of rodents. The projects in our sample included research performed at seven DOD laboratories and

seven non-DOD facilities. Twelve of the 24 projects were sponsored by the Army; 5 were sponsored by the Navy; and 7 were sponsored by Defense agencies (the Armed Forces Radiobiology Research Institute, the Defense Advanced Research Projects Agency, and the Uniformed Services University of the Health Sciences). Air Force projects were not included because the BRD did not list the Air Force as a sponsor of projects in these areas of research.

We visited the 14 facilities where the 24 projects were conducted (see table I.1).

**Table I.1: Research Facilities Included in Study**

Funding agency or department in parentheses

<b>Facility</b>	<b>Location</b>	<b>Number of projects</b>
<b>Department of Defense facilities</b>		
Armed Forces Radiobiology Research Institute	Bethesda, Maryland	3
U.S. Army Institute of Surgical Research	San Antonio, Texas	4
U.S. Army Medical Research Institute of Infectious Diseases	Frederick, Maryland	3
Naval Medical Center	San Diego, California	1
Naval Medical Research Institute	Bethesda, Maryland	2
Uniformed Services University of the Health Sciences	Bethesda, Maryland	2
Walter Reed Army Institute of Research	Washington, District of Columbia	2
<b>Non-DOD facilities</b>		
Childrens Hospital Medical Center (Defense Advanced Research Projects Agency)	Cincinnati, Ohio	1
Massachusetts General Hospital (Army)	Boston, Massachusetts	1
Naval Blood Research Institute, Boston University (Navy)	Boston, Massachusetts	1
University of Arizona (Army)	Tucson, Arizona	1
University of North Carolina (Army)	Chapel Hill, North Carolina	1
University of Tennessee Health Sciences Center (Navy)	Memphis, Tennessee	1
University of Virginia (Defense Advanced Research Projects Agency)	Charlottesville, Virginia	1

We reviewed documentation for each project to assess the protocol development and review processes. The review included acquiring and reviewing each research project's animal use protocol; Institutional Animal Care and Use Committee (IACUC) records for these protocols; IACUC correspondence; institutional policies, procedures, and training materials; and correspondence between DOD reviewing officials and the investigator. Among those we interviewed at the facilities were past and current IACUC chairs, attending veterinarians, and other officials. We also interviewed investigators of 18 of the 24 research projects and nonaffiliated IACUC members at 11 of the 14 facilities.

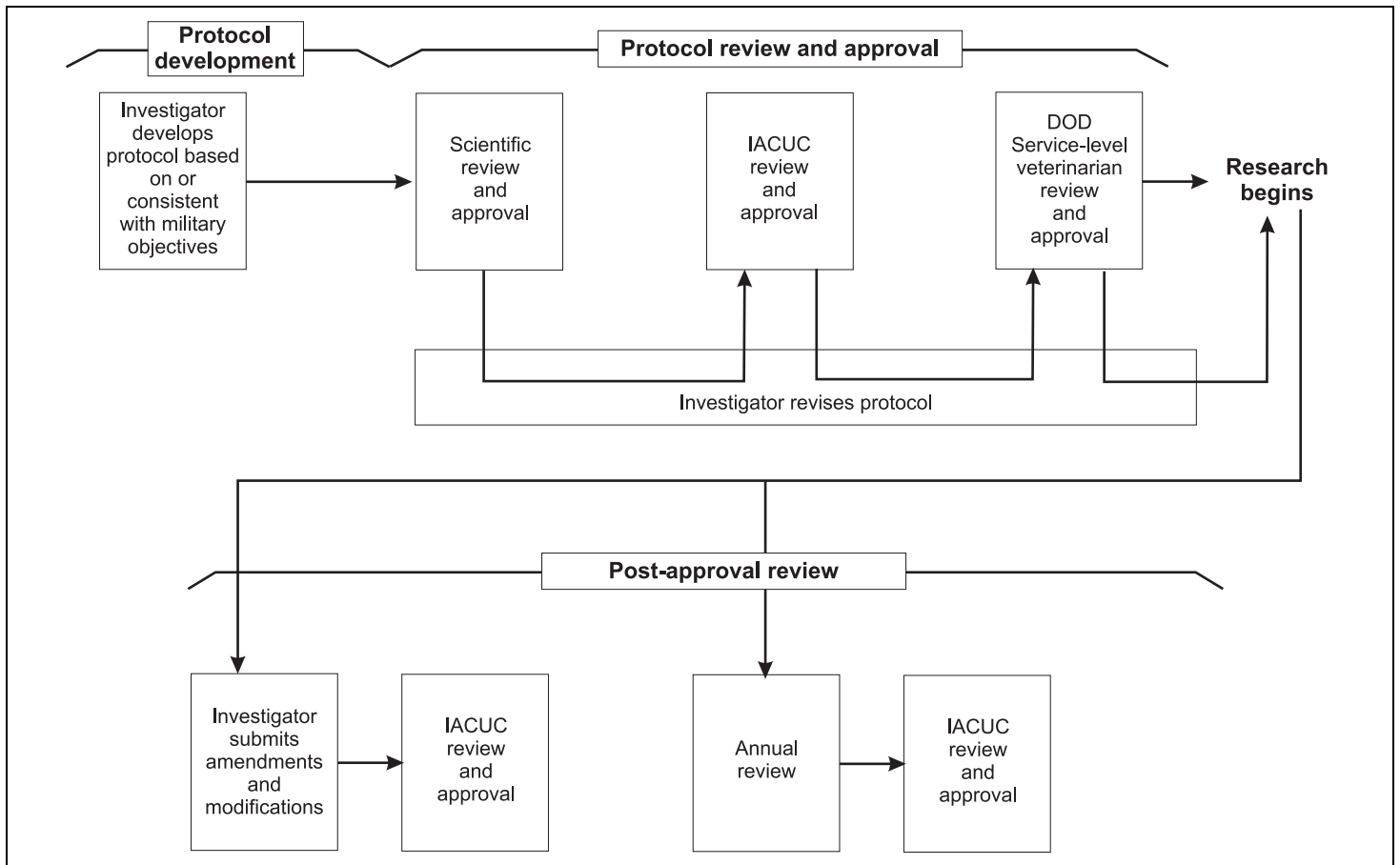
We contracted with the USDA's Animal Welfare Information Center (AWIC) to obtain an independent search of scientific literature relevant to each project. Each project was reviewed by three experts. We contracted with four subject matter experts, who reviewed projects in their areas of expertise. Also, we contracted with an expert in laboratory animal medicine and an expert in the field of alternatives to review all the projects. For each project, the experts reviewed research protocols, related documents, and the AWIC literature search. They provided comments that we considered when developing our findings on unnecessary duplication and alternatives. Our findings are not generalizable to all DOD research that used animals in fiscal year 1996.

We performed our work from October 1997 to May 1999 in accordance with generally accepted government auditing standards.

# DOD's Process for Reviewing Animal Research Proposals

DOD's process to reduce unnecessary duplication and promote alternatives to animal use relies on investigators to prepare detailed plans of their research—called protocols—and several levels of review of these protocols (see fig. II.1). The facilities we visited generally followed similar practices, with minor variations.

Figure II.1: DOD's Process for Reviewing Animal Research Protocols in Fiscal Year 1996



## Protocol Development

In October 1995, DOD implemented a standardized protocol format for use by its facilities and required non-DOD facilities to address the information contained in the format. DOD implemented this format in response to recommendations by the Inspector General, who found that each research facility differed in the information it collected on proposed research. Of

the 24 studies we reviewed, 4 of the 5 that were developed after October 1995 used the new protocol format. The other protocols were developed prior to 1995 and used different formats.

The standard protocol format requires that investigators address several elements, including the study background, objectives and hypotheses, military relevance, experimental design, animal requirements and justifications, research procedures, veterinary care, investigator qualifications, and safety issues. In the protocols, investigators are required to provide written assurance that the proposed research does not unnecessarily duplicate other studies. This requirement stems from animal welfare regulations. In addition, DOD requires that its investigators review specific electronic databases to identify whether the proposed research could unnecessarily duplicate other studies; document the results of their search; and identify the databases searched, key words used, and the dates of the search. Investigators must present written justification for the use of animals, to include consideration of nonanimal alternatives, the total number and species of animals to be used, and alternatives being employed.

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## **Review and Approval of Animal Use Protocols**

DOD requires that each protocol pass through several review steps before animals are used: a scientific review, a facility-level review by an IACUC and, for many protocols, a DOD veterinary review. A scientific merit review is conducted by the DOD funding organization to determine whether the research is likely to contribute to the advancement of scientific knowledge and military objectives. Generally, scientific merit reviews for DOD facilities are conducted by in-house scientists. Scientific merit review for research at non-DOD facilities varies depending on the funding agency. For example, the U.S. Army Medical Research and Materiel Command conducts scientific merit reviews for projects proposed by investigators at non-DOD facilities by contracting with scientists who are not affiliated with the command or the facility. On the other hand, the Office of Naval Research uses in-house scientists to conduct scientific reviews of its research at non-DOD facilities.

Proposals that pass scientific review are then reviewed by the research facility's IACUC. The IACUC review is critical to the entire process because IACUC approval is required before funding is allocated and animals can be ordered or used. The IACUC conducts a review of the protocol to ensure compliance with animal welfare laws and regulations. Although minutes of the review meetings are maintained, detailed

documentation of issues discussed in the consideration of protocols is not required.

Under certain circumstances, DOD requires a third level of review. If a proposal calls for using nonhuman primates, DOD requires that a service-level veterinarian trained or experienced in laboratory animal science and medicine perform a review. The purpose of this review is to ensure that the investigator and the institution where the research is to be conducted are in compliance with the Department of Health and Human Services' guidance on the supply and use of laboratory primates.<sup>1</sup> In addition, DOD requires that these reviewers examine all projects at non-DOD facilities, regardless of the species used, for compliance with animal welfare and DOD requirements. The Army requires a similar type of review for protocols at its facilities that propose to use dogs or cats.

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## **Post-approval Review of Research**

Once the research has begun, the IACUC annually reviews each protocol. The purpose of the annual review is to determine whether the project should continue. The annual protocol report describes the project's status (e.g., active, terminated) and any significant changes made to the protocol during the year. In addition, if investigators wish to amend the protocol during implementation of their research, they must obtain approval from the IACUC before making changes. The nature of the IACUC's review depends on the significance of the change. IACUCs often delegate approval for minor modifications such as a change in the dosage of a drug being administered to the veterinarian member of the IACUC. A major modification such as a change in number of animals to be used generally necessitates a formal review by the IACUC.

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<sup>1</sup> National Primate Plan, U.S. Department of Health and Human Services, NIH-80-1520 (Oct. 1978).



# Comments From the Department of Defense



DIRECTOR OF DEFENSE RESEARCH AND ENGINEERING  
3030 DEFENSE PENTAGON  
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JUN 11 1999

Mr. Kwai-Cheung Chan  
Director, Special Studies and Evaluation  
National Security and International  
Affairs Division  
U.S. General Accounting Office  
Washington, DC 20548

Dear Mr. Chan:

Attached is the Department of Defense (DoD) response to the General Accounting Office (GAO) draft report, "DoD Animal Research: Controls on Animal Use are Generally Effective But Improvements Are Needed," dated May 21, 1999 (GAO Code 713013/OSD Case 1703-A).

The DoD is concerned about the title of the GAO Report, especially about the term "needed". The DoD acknowledges that there is room for improvement in the controls placed on animal use within sponsored programs. However, the term "needed" implies that improvements are required or necessary to meet a standard. The GAO Report identifies no instances where a DoD Animal Care and Use Program failed to meet the federal standards established by the Animal Welfare Act or its implementing regulations. The DoD therefore requests that the GAO re-title this report. A suggestion for the title would be to replace the word "Needed" with the word "Suggested". The title would then read: "DoD Animal Research: Controls on Animal Use are Generally Effective But Improvements are Suggested".

The DoD has provided technical corrections to the GAO under separate cover. If you have any questions, please call CDR Ed Lane at (703) 601-1724.

*Hans Mark*  
Hans Mark



**Appendix III**  
**Comments From the Department of Defense**

Response to GAO DRAFT REPORT dated May 21, 1999  
(GAO CODE 713013 OSD CASE 1703-A)

“DOD ANIMAL RESEARCH: CONTROLS ON ANIMAL USE ARE GENERALLY  
EFFECTIVE BUT IMPROVEMENTS ARE NEEDED”

DEPARTMENT OF DEFENSE COMMENTS TO  
THE GAO RECOMMENDATIONS

RECOMMENDATION 1: To further reduce the likelihood that proposed research unnecessarily duplicates other research, the GAO recommended that the Secretary of Defense clarify policy regarding the databases of research in progress that investigators must search. (p. 29/GAO Draft Report)

Now on p. 19.

DOD RESPONSE: Concur. The Department recognizes that in spite of the significant efforts to meet the Congressionally requested improvements in DoD’s controls over research using animals, additional clarification of policy could be beneficial. Therefore, the Department will provide additional clarification regarding the databases of research in progress.

RECOMMENDATION 2: The GAO recommended that the Secretary of Defense further facilitate the consideration of refinement alternatives by investigators and institutional animal care and use communities. Specifically, the GAO recommended that the DoD standard animal use protocol form should be amended to require investigators to identify refinement alternatives that were considered but not adopted, and explain why they were not adopted. (pp. 2-30/GAO Draft Report)

Now on p. 19.

DOD RESPONSE: Concur. The Department is committed to meet the requirements of the Animal Welfare Act. In this regard, the Department has established an Animal Use Committee Joint Technical Working Group, an annual Report to Congress on DoD’s use of animals in research, a standardized animal use protocol, animal use information in DTIC and updated animal use policy in DoD Directive 3216.1. The Department will amend the standard animal use protocol form to require investigators to identify refinement alternatives that were considered but not adopted and explain why they were not adopted.

# GAO Contacts and Staff Acknowledgements

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## GAO Contacts

John Oppenheim, (202) 512-3111  
Bruce D. Layton, (202) 512-6837

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## Acknowledgements

In addition to those named above, Jaqueline Arroyo, Dan Engelberg, Cary Russell, and Gregory Whitney made key contributions to this report.

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# Related GAO Products

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DOD Animal Research: Improvements Needed in Quality of Biomedical Research Database (GAO/NSIAD/HEHS-99-24, Dec. 14, 1998).

Biological Warfare: Better Controls in DOD's Research Could Prevent Unneeded Expenditures (GAO/NSIAD-91-68, Dec. 27, 1990).

Army Biomedical Research: Concerns About Performance of Brain-Wound Research (GAO/HRD-91-30, Dec. 12, 1990).

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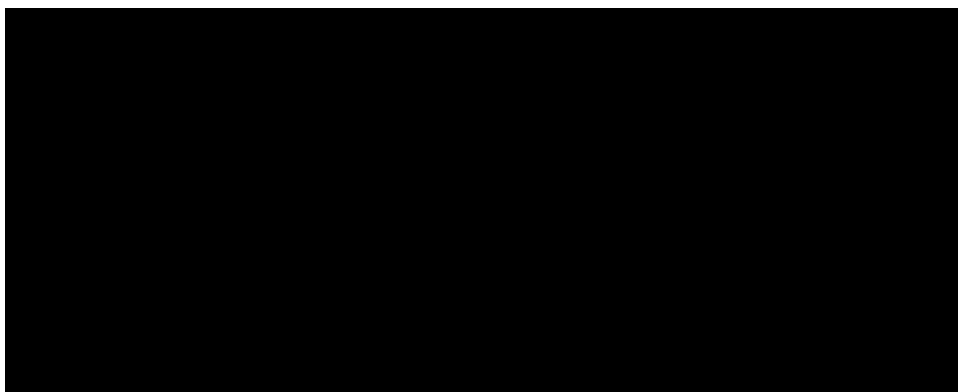
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