

Overview

The National Institutes of Health System for Enhancing the Science, Safety, and Ethics of Recombinant DNA Research

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Oversight of recombinant DNA research by the National Institutes of Health (NIH) is predicated on ethical and scientific responsibilities that are akin, in many ways, to those that pertain to the oversight of animal research. The NIH system of oversight, which originated more than 25 years ago, is managed by the NIH Office of Biotechnology Activities (OBA), which uses various tools to fulfill its oversight responsibilities. These tools include the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* and the Recombinant DNA Advisory Committee. The OBA also undertakes special initiatives to promote the analysis and dissemination of information key to our understanding of recombinant DNA, and in particular, human gene transfer research. These initiatives include a new query-capable database, an analytical board of scientific and medical experts, and conferences and symposia on timely scientific, safety, and policy issues.

Veterinary scientists can play an important role in the oversight of recombinant DNA research and in enhancing our understanding of the many safety and scientific dimensions of the field. These roles include developing appropriate animal models, reporting key safety data, enhancing institutional biosafety review, and promoting compliance with the *NIH Guidelines*.

The ethical and scientific basis for oversight

A basic tenet guiding responsible research with animals is to promote the health and welfare of animal subjects by observing the principles, regulations, and guidelines that govern their use. There are several justifications for this tenet. First and foremost, it is an ethical responsibility predicated on respect for living things. Second, adherence to this principle is key to good science; properly maintained animals are healthier and more consistent in their physiology, allowing better modeling of biological processes, pathology, and pharmacokinetics.

A similar tenet applies to recombinant DNA research. Scientists have an abiding responsibility to follow the principles of containment and safe practices that the National Institutes of Health (NIH) has outlined. This is an ethical responsibility derived from obligations to consider the risk of one's work and to avoid harm to human health and the environment. That notwithstanding, there also is a scientific rationale. Adhering to the guidelines and requirements associated with recombinant DNA research promotes the integrity of research materials and practices—necessary for good science.

The NIH, too, has ethical and scientific duties in this arena. Having the NIH assume major oversight responsibility was ethically appropriate, given that the agency funded and continues to support research developing and using recombinant DNA tools and techniques. As a steward of the public monies used for

this purpose, it is incumbent on the agency to ensure that those funds are awarded to entities that will expend them safely and responsibly. Furthermore, the NIH system of oversight promotes the exchange of vitally important scientific information. This enables high-quality research and helps advance all fields of science using recombinant DNA.

Components of NIH recombinant DNA oversight

Responsibility for NIH oversight of recombinant DNA research is shouldered by the NIH Office of Biotechnology Activities (OBA), which is located within the Office of Science Policy, a key component of the Office of the Director of the NIH. Simply stated, the role of the OBA is to implement and manage the various oversight tools and information resources that NIH uses to promote the science, safety, and ethics of recombinant DNA research. The key tools of biosafety oversight are the *NIH Guidelines for Research Involving Recombinant DNA Molecules*, institutional biosafety committees (IBCs), and the NIH Recombinant DNA Advisory Committee (RAC). Through the information resources it creates and manages, OBA further enhances safety and scientific understanding through analysis and dissemination of information to the scientific community and public at large. This is accomplished through initiatives, such as scientific safety symposia and policy conferences, the Genetic Modification Clinical Research Information System, and a planned Gene Transfer Safety Assessment Board. These tools and initiatives will be described in more detail.

The *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)*. The *NIH Guidelines*

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Table 1. *NIH Guidelines for Research Involving Recombinant DNA Molecules*
 Summary of the Review Requirements Highlighting Animal Research

Level of review	Example of general recombinant DNA research	Relevant section(s) of the <i>NIH Guidelines</i>	Example of recombinant DNA research involving whole animals	Relevant section(s) of the <i>NIH Guidelines</i>
Exempt from the <i>NIH Guidelines</i> and IBC registration not required if experiment not covered by Sections III-A, III-B, or III-C	Recombinant DNA molecules that (1) are not in organisms or viruses; (2) consist entirely of DNA segments from a single nonchromosomal or viral DNA source; (3) consist entirely of DNA from a prokaryotic host when propagated in that host; (4) consist entirely of DNA from a eukaryotic host when propagated in that host; (5) consist of DNA from different species that exchange DNA through known physiologic processes; (6) do not present risk to health or environment as determined by NIH Director	III-F	Purchase or transfer of transgenic rodents for experiments that require BL-1 containment	III-D-4-c-(2), Appendix C-VI
IBC notice at initiation	Experiments in which all components derive from non-pathogenic organisms (and other experiments not included in Sections III-A, III-B, III-C, III-D, III-F)	III-E	Creating stable germline alterations of rodents using recombinant DNA when these experiments require only BL-1 containment	III-E-3
IBC approval before initiation	Experiments using higher risk organisms (Risk Group 2-4) as DNA source or host-vector system	III-D	Creating stable germline alterations of an animal's genome, or testing viable rDNA modified microorganisms on whole animals, where BL-2 containment or greater is necessary	III-D-4
IBC and IRB approval, NIH RAC review	Experiments involving the deliberate transfer of recombinant DNA to humans	III-C	Not applicable	Not applicable
IBC approval and NIH review for containment determinations	Experiments involving the cloning of toxin molecules with an LD50 of < 100 ng/kg for vertebrates; or transfer of recombinant DNA from or to restricted agents	III-B-1, III-D-1-d, III-D-2-b, III-D-3-d	Experiments conducted with a recombinant DNA modified restricted agent in a whole animal	III-D-1-d
IBC, RAC review, and NIH Director review and approval	Experiments involving the deliberate transfer of a drug resistance trait to microorganisms, not known to acquire it naturally, that could compromise control of disease agents	III-A	Experiments that compromise the control of disease agents in veterinary medicine through deliberate transfer of a drug resistance trait	III-A-1-a

(1) are the cornerstone of the NIH's system of oversight. They specify scientifically based principles for the review and containment of various forms of recombinant DNA research. They also articulate the responsibilities of institutions, investigators, institutional biosafety committees, biosafety officers, and even the NIH Director in the oversight of recombinant DNA research.

The *NIH Guidelines* were first developed over 25 years ago as an outcome of a process by which scientists assumed responsibility for managing the risks of their own research activities by closely examining the potential hazards and defining the necessary oversight of what was then a nascent and poorly understood technology. This process included a July 1974 report from the Committee on Recombinant DNA Molecules of the National Academy of Sciences that called for a voluntary moratorium on certain types of "high risk" experimentation and the development of guidelines for the conduct and review of recombinant DNA research (2). In February 1975, scientists convened the landmark "Asilomar" conference to examine the science and safety of this technology. Participants at that event reaffirmed the value of such guidelines (3). When first fleshed out a year later, the *NIH Guidelines* embodied a scientifically based approach to the oversight of recombinant DNA research. Since their origin, they frequently have been revised in accordance with our understanding of the science and potential risks of this area of activity.

The *NIH Guidelines* apply to any project involving recombinant DNA that is conducted at or sponsored by an entity that receives NIH support for recombinant DNA research (4). This is

an important and often not well-understood point. Even if a project is entirely privately funded, it is subject to the *NIH Guidelines* if any investigator at the institution or the company funding the project has a grant or contract from the NIH supporting recombinant DNA research. The logic for this broad applicability is that, to be effective, biosafety principles must be observed by all researchers at a given facility.

In addition, the *NIH Guidelines* apply to research that involves testing in humans of materials containing recombinant DNA developed with NIH funds, if the institution that developed those materials sponsors or participates in those projects. In this instance, the objective is to ensure that proper practices are used in an area of research where NIH has clear involvement and safety is a paramount consideration.

The *NIH Guidelines* are termed "guidelines" because they offer principles and basic safety practices without being overly prescriptive. The title of the document is not meant to convey, however, that they are optional. Compliance with the *NIH Guidelines* is an important term and condition of NIH funding (5). An institution or investigator that disregards them is placing the institution at risk of special oversight or even a loss of eligibility for NIH funding of recombinant DNA research.

Administrative and review responsibilities. The *NIH Guidelines* have two important components: the body and the appendices. The body of the document specifies administrative and review responsibilities that institutions and investigators assume when they receive NIH funds for recombinant DNA re-

search. The body also outlines the levels of institutional and federal review that are necessary for various types of recombinant DNA research. As the risk of the research increases, higher levels of review and approval are necessary. Table 1 presents the levels of review that will be required for several forms of experimentation involving recombinant DNA.

Appropriate review generally involves an examination of the proposed experimentation by an institutional biosafety committee (IBC), the roles and responsibilities of which are described in detail in a subsequent section of this article. For many low-risk experiments, investigators may simply notify the IBC at initiation of the experiment. Other experiments involve full IBC review and approval prior to initiation. Human gene transfer research requires IBC review and approval and RAC review. The Institutional Review Board (IRB) also must review and approve this research. For certain types of high-risk experiments, NIH review, and in rare cases, review and approval by the NIH Director is necessary.

The IBC is charged with helping investigators determine the appropriate containment conditions in which to conduct their projects. The IBC is guided by one of several appendices in the *NIH Guidelines* that specify safety and containment practices for various forms of recombinant DNA research. In many respects, these appendices serve as the heart of the document for basic research, and their observance is critical to the effectiveness of the *NIH Guidelines* as a tool for promoting institutional oversight and biosafety.

Key appendices for veterinary scientists are:

Appendix G—Most animal research involves rodents or other small animals, which are generally used under laboratory conditions. When recombinant DNA research (including that using small animals) is being performed in the laboratory, Appendix G of the *NIH Guidelines* applies. Appendix G outlines four levels of laboratory containment for recombinant DNA research that range from biosafety level (BL-1) (general laboratory conditions and practices) to BL-4 (which entails highly restricted access, airlocks with negative pressure, and other significant safety and security measures). Some representative characteristics and practices associated with each biosafety level are outlined in Table 2.

Appendix M—This appendix provides points to consider in the design and submission of human gene transfer experiments and is key to helping investigators promote the safety and welfare of participants in clinical research. Although it is focused on research with people, not animals, it is nonetheless worthy of the attention of veterinary scientists since several sections of this appendix touch on the importance of data from animal experiments for human trials.

Appendix Q—This appendix specifies practices for the physical and biological containment of large animals:

- whose genome has been altered by the stable introduction of recombinant DNA, or DNA derived there from, or
- that are used in experiments involving viable recombinant DNA-modified microorganisms.

This appendix supercedes Appendix G when research animals are of a size or have requirements that preclude use of laboratory containment (e.g., cows, pigs, sheep). Appendix Q also includes four levels of containment (BL1-N to BL4-N) that are increasingly stringent according to the nature of the research. Many of the practices described in Appendix Q are

Table 2. Summary of biosafety level characteristics and practices

Biosafety level	Representative characteristics and practices*
BL-1	Standard microbiological and laboratory practices: -Decontamination of work surfaces -Mechanical pipetting -Hand washing after handling recombinant DNA -Food storage in specially designated areas -Appropriate protective clothing
BL-2	BL-1 practices, plus: -Biosafety manual prepared and adopted for laboratories -Biological safety cabinets (I or II) for work creating aerosols -Limited access to laboratory -Hazard warning sign on door -Laboratory clothing not worn outside laboratory -Laboratory waste decontaminated -Spills and accidents reported to IBC and OBA
BL-3	BL-2 practices, plus: -Separation of laboratory from open access areas -Water-resistant walls, floors, ceilings -Impervious benchtops -Closed and sealed windows -Biosafety cabinets necessary for recombinant DNA work -Molded surgical masks necessary for animal work -High-efficiency particulate air/HEPA filters -Liquid disinfectant traps
BL-4	BL-3 practices, plus: -Maximum containment facility -Facility has sealed internal shell -Unique air supply and exhaust system -Greatly restricted access to facility -Secured, locked doors; sign-in log -Entrance to facility through clothing-change and shower rooms -Airlocks, negative air pressure in laboratory -Class-III biosafety cabinets, or class I or II with positive pressure suits -Nonbreakable, sealed, decontaminated containers for movement of materials out of class-III cabinets, or maximum containment laboratories -Decontamination dunk tanks

*These are not complete, but are intended to give a general sense of the level of containment typical of each biosafety level.

tailored to animal facilities and address appropriate handling and disposal of biological specimens, waste, and euthanized animals.

Institutional Biosafety Committees. Researchers who use animals are accustomed to submitting their research proposals to institutional animal care and use committees (IACUCs). They may be less cognizant, however, that when these proposals entail recombinant DNA, they must also be submitted to the IBC. Institutional biosafety committees were established through the *NIH Guidelines* for local review of recombinant DNA research. Under the *NIH Guidelines*, they are assigned specific responsibilities.

The IBCs review proposed experimentation with recombinant DNA to ensure that it is safely contained in a manner consistent with the biosafety levels and practices outlined in the *NIH Guidelines*. Equally important, IBCs assess the adequacy of facilities, institutional procedures and practices, and investigator training and expertise for this type of research. When human gene transfer trials were first proposed just over a decade ago, IBCs assumed additional responsibilities for reviewing clinical protocols to ensure the safety and proper design of this research. These responsibilities included receipt and analysis of adverse event reports and findings from animal studies germane to the design and conduct of human trials. Finally, many

institutions have assigned these committees authority and responsibilities that extend beyond their mandate under the *NIH Guidelines*, which often includes the oversight of research involving other biohazardous materials, such as carcinogens and infectious agents.

The IBCs must have at least five members, and collectively the members must have appropriate expertise to review recombinant DNA research. As is true of IACUCs, IBCs must include individuals not affiliated with the institution. Although IACUCs are only required to have one such individual, IBCs, according to the *NIH Guidelines*, are required to have a minimum of two. These individuals provide public participation in the review process, representation of community attitudes, and consideration of community health and environmental concerns. When the institution is conducting recombinant DNA research involving whole animals too large to use in normal laboratory conditions, the IBC must include an expert in animal containment. In general, veterinary science expertise is always of value in analysis of data and reports emanating from animal studies.

The NIH Recombinant DNA Advisory Committee. The RAC was first formed at the conclusion of the 1975 Asilomar conference (6). The RAC is advisory to the NIH Director through OBA. As is true of the *NIH Guidelines*, the role of the committee has evolved with the science and understanding of this technology. The RAC once reviewed and recommended approval of all experiments involving recombinant DNA. As the risk profile of various forms of experimentation was better understood and deemed to be low, experiments were gradually “grandfathered” in, no longer requiring RAC review. Today, the RAC is a reservoir of expertise on many important biosafety and policy matters concerning the conduct of various kinds of recombinant DNA research. It also reviews human gene transfer protocols with a focus on the science, safety, and ethics of this activity.

Specific materials concerning proposals for human gene transfer trials subject to the *NIH Guidelines* must be submitted to the NIH so that the OBA Director, on the advice of the RAC, can determine which studies warrant in-depth review and public consideration. These generally are protocols that are notable due to the novelty of the approach or to special safety or ethical considerations. The RAC meeting is convened for this public discussion on a quarterly basis. At the meeting, which any interested member of the public may attend, the investigator presents the details of his or her proposed experiment. The RAC members and invited experts pose questions and make observations, findings, and recommendations as appropriate. A final set of recommendations is voted on at the end of the meeting and is conveyed to the investigator, the IBC, the IRB, and the FDA in writing.

In its review of human studies, the RAC is guided by Appendix M of the *NIH Guidelines*. Animal studies are a necessary precursor to human gene transfer trials (as is true of most clinical trials) to provide proof of principle and to study the safety, toxicity, biodistribution, efficacy, and other characteristics of the product being evaluated. Pursuant to recent amendments to the *NIH Guidelines*, Appendix M and the RAC give substantial attention to animal studies and explicitly emphasize the need to report data from animal studies that may point to risks to humans (7, 8). In evaluating human trials, the RAC focuses on a number of questions concerning the validity and applicability of animal models, including:

- What animal models were used in laboratory studies to as-

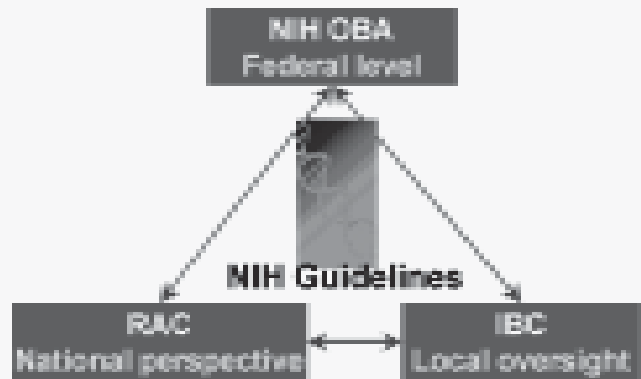


Figure 1. Schematic of how the major components of the National Institutes of Health (NIH) system for enhancing the science, safety, and ethics of recombinant DNA research oversight relate to one another.

sess *in vivo* efficacy of the gene transfer system?

- In what ways are the animal models used similar or different from humans?
- Do the animal models used reflect human pathology and physiology for the disease and organ system being studied?
- What animal studies have been conducted to determine whether there are pathologic or other undesirable consequences of the protocol?
- Do animal studies indicate that vector DNA has entered non-targeted cells (including germ cells)?
- If a retrovirus delivery system is being used, is there any evidence that the retroviral vector has recombined with any endogenous or other viral sequences in the animals?
- How long have animals been studied after the experimental intervention (to explore such concerns as tumorigenicity)?

Figure 1 provides a schematic of how the components of this system of oversight fit together. The *NIH Guidelines* are the backbone of the system, which NIH OBA manages. The IBCs provide a mechanism by which this oversight extends down to the local level. The RAC, on the other hand, provides oversight and guidance with a national perspective.

As represented by the arrows, information flows in all directions among the three major organizational components. The IBCs submit membership reports and other information to OBA, which provides IBCs with much needed information about the field. The IBCs are often the first to identify emerging safety issues and policy concerns, which are then presented to the RAC. The RAC review of human gene transfer protocols yields information of critical importance to IBC oversight and review responsibilities. Finally, OBA provides the RAC with the protocols and additional information it needs to make its assessments, whereas the RAC advises and informs OBA about the field and its oversight role.

Information and analytical resources

The OBA has a number of initiatives underway to enhance accessibility and scientific value of the information that it gathers and makes available to the public. These initiatives include scientific symposia and policy conferences, a national database of human gene transfer trials, and a board to analyze safety data.

Scientific symposia and policy conferences. In 1999, the NIH initiated, also in collaboration with the FDA, a series of

gene transfer safety symposia to explore specific issues in the safety of gene transfer trials. These symposia bring together leading experts in various facets of gene transfer research to explore scientific and medical issues germane to salient concerns about this area of clinical investigation. One symposium, held subsequent to the death of a gene transfer trial participant, permitted an in-depth, public exploration of the safety and toxicity of the type of viral vector—an adenovirus—used in that experiment, with the objective of enhancing knowledge about the safety profile for this vector system so that future clinical trials could be appropriately designed. The report of that meeting has been published and is available to the general public on the NIH Web site (9). It outlines important recommendations for the conduct of preclinical and clinical studies, as well as on obtaining informed consent and developing a reference standard to assess the potency and quality of products using this vector.

A more recent symposium focused on safety concerns that arose from animal studies of adeno-associated viral (AAV) vectors, which also are commonly used in gene transfer trials. A study using a murine model suggested that AAV—a virus not known to cause disease in humans—might lead to tumor production, which raised appreciable concerns for human trials. The symposium allowed investigators to share quickly and efficiently the latest pertinent scientific findings and to establish that the phenomenon observed in the mouse study could not be generalized to human studies. Other recent symposia have provided an opportunity for in-depth analysis of adverse events that occurred in a trial studying involving gene transfer approaches to treating X-linked severe combined immunodeficiency.

In addition to these scientific symposia, OBA has sponsored various policy conferences, as well, that have looked at such matters as inadvertent germline gene transfer, prenatal use of gene transfer, and the evolving roles of IBCs.

Genetic Modification Clinical Research Information System (GeMCRIS). Several years ago, OBA developed a pilot database of gene transfer trials that, until recently, was available to the public on its Web site (10). This database initially contained basic information about the trials, including an abstract; the name of the gene transfer product, investigator, institution, and sponsor; and the targeted disease. To enhance the usefulness and accessibility of these data, OBA, in collaboration with the Food and Drug Administration (FDA), developed GeMCRIS, a major enhancement to the existing database. The GeMCRIS is query capable, using a standard medical vocabulary and a genetic element vocabulary developed specifically for gene transfer research. It enables on-line adverse event reporting for investigators and interfaces with other major adverse event reporting systems. The GeMCRIS also has on-line search capability for public users who may wish to learn more about the use of a particular vector or gene transfer approaches being studied for specific diseases. The GeMCRIS will be accessible to the general public in the summer of 2003.

Gene Transfer Safety Assessment Board (GTSAB). As part of its mandate to oversee the safety of human gene transfer trials, the NIH conducts assessments of serious adverse events that may be important for the health and safety of those who volunteer to participate in these trials. Toward that end, the NIH plans to establish a new analytical panel, the GTSAB, which will conduct a comprehensive review of serious adverse event data accumulated from gene transfer trials being con-

ducted across the country. It will be composed of experts in medicine, statistics, clinical research design, and other relevant specialties. The GTSAB will be a systematic and publicly accountable mechanism for the review and assessment of toxicity and safety data from clinical trials using recombinant DNA products. It will greatly enhance the ability to identify trends and recognize patterns that may have important implications for the future development of human gene transfer research. It will provide reports to the RAC at its public meetings, and thereby, promote open discussion of information about gene transfer research. The GTSAB was conceptualized and advocated by an *ad hoc* working group of clinicians and scientists from multiple NIH Institutes that fund and have program oversight responsibilities for gene transfer research. It will be staffed by OBA and involve close collaboration with the FDA.

Veterinary scientists and oversight of gene transfer research

Animal research and animal models will continue to be key to development of human gene transfer techniques because, compared with other fields of human investigation, this is still a relatively new endeavor, with many scientific and safety questions in need of exploration. A specific challenge will be to find the most appropriate animal models for studying these issues. This will be important for predicting the human experience with gene transfer products and, thus, essential for enabling scientists to minimize risks to research participants. Furthermore, laboratory animals are costly to procure and properly maintain; thus, finding the right models will allow more efficient use of this valued resource.

Veterinary scientists have particularly important roles to play in the advancement of this field, as key agents in the process of moving research findings from bench to bedside. Specifically, veterinary scientists are key to:

Developing appropriate animal models for preclinical studies—Veterinary scientists have a key role in the assessment of animal studies and in relating findings to the design and conduct of human studies.

Reporting safety data—Veterinary scientists are first-line “safety sentinels” by virtue of their role in identifying and notifying colleagues of animal experiments that suggest a substantial risk to humans. The need for such information has been recently augmented with explicit inclusion of this type of preclinical data in the safety reporting requirements found in the *NIH Guidelines*.

Enhancing institutional biosafety—Veterinary scientists are experts in areas key to the promotion of biosafety and containment of risks. They have special expertise and important contributions to make to discussions of animal containment, zoonotic disease, evaluations of risk levels, and other matters.

Promoting compliance—Under the *NIH Guidelines*, institutions must report significant problems, violations, or any significant research related accidents and illness to NIH OBA within 30 days. Veterinary scientists can be among the first to become aware of such matters and help ensure that they come to the attention of the IBC and other institutional officials who, in turn, will report them to OBA.

The OBA wishes to aid veterinary scientists in serving these roles. Toward that end, OBA can be a resource on a number of issues:

Interpretations of the *NIH Guidelines*—The OBA staff members are poised to respond to any queries concerning the interpretation and application of the *NIH Guidelines*. Staff members regularly field questions concerning appropriate containment for various recombinant DNA constructs, the submission process for human gene transfer protocols, and requirements that pertain to IBCs.

Information resources—The OBA is a repository of information concerning recombinant DNA research and, especially, human gene transfer trials. Because the NIH oversight process is a transparent one, clinical investigators in this field submit protocols in the knowledge that they will be publicly discussed and available. Furthermore, OBA is enhancing its analytical capabilities through the launching of GeMCRIS. Information about trials using specific vectors or targeting particular diseases will be readily accessible. Future iterations of this system will include preclinical toxicity data. The planned GTSAB will add an unprecedented analytical capacity to our understanding of adverse events. Finally, OBA sponsors gene transfer policy conferences and safety symposia to promote the dialogue and understanding about developments in this field.

Accessibility is a hallmark of how OBA functions, and scientists, administrators, and other members of the public are encouraged to contact us by phone, e-mail, or in writing. Our contact information may be found at the end of this article.

Conclusions

The NIH system of oversight of recombinant DNA research is predicated on several imperatives that the agency faces as the largest funder of biomedical research. The NIH, as a steward of public funds, has an important fiduciary responsibility over eventual uses of those funds. In addition to awarding them judiciously, through our well-established process of peer review, NIH must be confident that institutions will assume the appropriate stewardship of those monies. Thus, NIH must be assured that the institution has systems of oversight in place. For recombinant DNA research, that means that the institution and its investigators are fulfilling the responsibilities assigned to them under the *NIH Guidelines*. Part of that stewardship involves ensuring the safety of NIH-funded activities. Safety oversight, when properly carried out, should protect, from undue risk, researchers and laboratory staff who conduct recombinant DNA research, participants in clinical research, and the communities and environments in which they live and work.

The mission of the NIH is to promote discovery of new knowl-

edge that will lead to better health for everyone. Responsible science is good science and, thus, leads to quality research and research findings. Following the *NIH Guidelines* achieves that objective. That objective is further enhanced by the initiatives that OBA has undertaken to promote the quality, analysis, and dissemination of data on recombinant DNA research and, in particular, human gene transfer trials.

Veterinary scientists have a key role to play in helping NIH to fulfill these imperatives. The OBA wishes to work more closely with this community in the future and to enhance the ways in which we can serve as a resource for each other. The OBA and the veterinary science community can form a partnership to promote safe conduct and advancement of the field.

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References

1. <http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html>
2. **Berg, P., D. Baltimore, H. W. Boyer, S. N. Cohen, R. W. Davis, D. S. Hogness, D. Nathans, R. Roblin, J. D. Watson, S. Weissman, and N. D. Zinder.** 1974. Potential hazards of recombinant DNA molecules. *Science* **185(4148)**:303.
3. **Berg, P., D. Baltimore, S. Brenner, R. Roblin, and M. F. Singer.** 1975. Asilomar conference on recombinant DNA molecules. *Science* **188 (4192)**:991-994.
4. **NIH Guidelines.** Section I-C-1-a-(1).
5. **National Institutes of Health.** NIH Grants Policy Statement, March 2001; http://grants.nih.gov/grants/policy/nrhgps_2001/part_ia_1.htm#Toc504811790.
6. **National Institutes of Health, Department of Health, Education, and Welfare.** July 7, 1976. Recombinant DNA research: guidelines. *Fed. Reg.* **41(131)**:27901-27943.
7. Appendix M-II-B-2, Preclinical studies including risk assessment studies; http://www4.od.nih.gov/oba/rac/guidelines_02/Appendix_M.htm#_Toc7255857.
8. Appendix M-I-C-4, Safety reporting; http://www4.od.nih.gov/oba/rac/guidelines_02/Appendix_M.htm#_Toc7255846.
9. **Recombinant DNA Advisory Committee.** 2002. Assessment of adenoviral safety and toxicity: report of the National Institutes of Health Recombinant DNA Advisory Committee. *Human gene therapy* **13**:3-13; accessible on OBA's web site at: http://www4.od.nih.gov/oba/rac/adsat_rpt.pdf.
10. The pilot database was removed in preparation for the launching of the new GeMCRIS system. The same information is available in our list of submitted protocols that can be accessed at: <http://www4.od.nih.gov/oba/rac/PROTOCOL.pdf>.