ENVIRONMENTAL ASSESSMENT AND FINDING OF NO SIGNIFICANT IMPACT

Concerning a Proposed Modification of the National Institutes of Health Guidelines for Research Involving Recombinant DNA

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I. Introduction and Summary

This Environmental Assessment (EA) concerns Proposed Actions by the National Institutes of Health (NIH) to amend the *Guidelines for Research Involving Recombinant DNA Molecules* (*NIH Guidelines*). These proposed amendments to the *NIH Guidelines* concern changes in the NIH oversight of human gene transfer research. The current version of the *NIH Guidelines* is 59 FR 34496, amended 59 FR 40170, 60 FR 20726, 61 FR 1482, 61 FR 10004, 62 FR 4782.

Specifically, the NIH proposes to relinquish general approval responsibilities for individual recombinant DNA experiments involving human gene transfer. The Food and Drug Administration (FDA) already holds statutory authority for such approval. The intent of the Proposed Actions is to enhance the NIH mechanisms for scientific and ethical oversight of recombinant DNA activities. These enhancements include retaining and restructuring the Recombinant DNA Advisory Committee (RAC), convening Gene Therapy Policy Conferences (GTPCs), and maintaining and improving public access to information on human gene transfer research.

Consistent with the objectives of the Vice President's National Performance Review and the Government Performance and Results Act, the Proposed Actions eliminate duplication of Federal procedures for approval of human gene transfer research.

These proposed amendments to the *NIH Guidelines* are the result of multiple *Federal Register* announcements and subsequent public discussions initiated by the NIH Director and conducted over a period of 18 months. During this time, the NIH Director sought and received advice from a wide spectrum of interested parties, both public and governmental, on the preliminary and current proposals.

This EA analyzes the Proposed Actions to amend the *NIH Guidelines* and finds that they have no significant impact on the human environment.

These Proposed Actions do not change the overall purpose or effect of the *NIH Guidelines*. They will continue to allow the benefits of recombinant DNA research to advance the public health and will continue to safeguard the interests of workers and subjects involved in the research.

II. Authority

This EA of the Proposed Actions under the *NIH Guidelines* has been prepared by the NIH Office of Recombinant DNA Activities (ORDA) according to: (1) The National Environmental Policy Act of 1969, 42 U.S.C. 4321-4347, as amended; (2) The Council on Environmental Quality Regulations for Implementing the Procedural Provisions of the National Environmental Policy Act, 40 CFR Part 1508; and (3) the General Administration Manual of the Department of Health and Human Services (HHS), Chapter 30-60. Authority to approve such an EA and Finding of No Significant Impact (FONSI) was delegated to the NIH Director by the Acting Director, Office of Management, Public Health Service (PHS), in a June 2, 1980, memorandum to PHS Agency Heads, "Delegation of Authority for Carrying Out Responsibilities Under Revised Part 30 of the General Administration Manual, Environmental Protection." The October 1977 Environmental Impact Statement on the *NIH Guidelines* (DHEW Publication No. 1489) adequately describes the process by which the NIH exercises oversight of recombinant DNA research.

III. Objective of the NIH Actions

These Proposed Actions have dual objectives: (1) to increase the usefulness and productivity of public awareness and discussion of human gene transfer research; and (2) to comply with the Vice Presidents National Performance Review and the Government Performance and Results Act aimed at improving interagency coordination, thereby reducing duplication and bureaucratic procedures.

The first objective is being accomplished by restructuring and refocusing the NIH RAC, by convening the GTPCs, and by maintaining and improving public access to human gene transfer information.

The second objective will be accomplished by eliminating duplication between the FDA and the NIH of review and approval of individual human gene transfer experiments. The FDA has the regulatory authority

to allow such experiments to proceed under its Investigational New Drug (IND) regulations, 21 CFR, Subchapter D. Therefore, it is appropriate that the FDA is exclusively responsible for the safety and efficacy approval process for individual human gene transfer protocols.

IV. Background

A. Description of the NIH's Roles and Responsibilities Regarding Promulgation of Actions under the *NIH Guidelines*.

The *NIH Guidelines* are flexible, incorporating appropriate modifications as knowledge is gained. Adopting any change to the *NIH Guidelines* is considered a major action under the *NIH Guidelines*. To execute a major action, the NIH Director must first seek the advice of the RAC and provide an opportunity for public and Federal agency comment. Current and former RAC members and Federal agency representatives were consulted regarding these changes.

The *NIH Guidelines* have been amended 50 times since they were first published in the *Federal Register* on July 7, 1976 (41 FR 27902). The proposed changes addressed in this EA are a continuation of the many previous changes to the *NIH Guidelines*.

B. Events Leading to the Development of Proposed Actions Under the *NIH Guidelines*

A special task force was chartered in November 1993 by the Secretary of HHS to identify ways to expedite the discovery and development of treatments for human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS). The Proposed Actions resulted from progressive steps initiated over the past four years by this task force (the National AIDS Task Force on Drug Development, or AIDS Task Force) to streamline the submission, review, and approval of human gene transfer clinical trials. On July 18, 1994, the AIDS Task Force held an open meeting to identify barriers to AIDS drug discovery and recommended changes to eliminate any unnecessary overlap between the NIH and the FDA. As a result of deliberations at the meeting, the NIH and the FDA proposed a simultaneous submission process consisting of a single submission format. This proposal became known as the "Consolidated Review" process. Amendments incorporating this change to the *NIH Guidelines* were published in the *Federal Register* on August 23, 1994, and February 8, 1995 (59 FR 43426 and 60 FR 7630, respectively). On March 6, 1995, the RAC recommended adoption of the Consolidated Review process to the NIH Director. The NIH Director accepted the RAC's recommendation and published these changes as major actions under the *NIH Guidelines* in the *Federal Register* on April 27, 1995 (60 FR 20726).

Under the Consolidated Review process, the RAC review of individual human gene transfer experiments was considered necessary only if the experiment represented characteristics deemed worthy of a full public review and approval by the NIH Director, such as novel applications of human gene transfer, novel gene delivery systems, new patient population, patient protection, or ethical issues.

This progression was manifested in the initial *Notice of Intent* published in the *Federal Register* on July 8, 1996 (61 FR 35774). In this notice, the NIH Director stated the intent to take several actions to enhance the NIH mechanisms for scientific and ethical oversight of recombinant DNA activities. These actions were: (1) discontinuing the RAC; (2) relinquishing all approval responsibilities for human gene transfer experiments to the FDA; (3) establishing the Office of Recombinant DNA Activities Advisory Committee (OAC) to ensure public accountability for recombinant DNA research and relevant data; (4) limiting the membership of the OAC to 6-10 individuals, compared to the 25 members appointed to the RAC; (5) implementing GTPCs to provide a public forum for discussion of issues relevant to human gene transfer; and (6) continuing the ORDA data management process that provides the public with comprehensive data on human gene

transfer clinical trials, including adverse event reporting.

Consultation with the RAC, input from other Federal agencies, and comment from the public were essentia in the process leading up to these Proposed Actions. In response to the July 8, 1996, "Notice of Intent," the NIH received a variety of comments reflecting a broad spectrum of public opinion. The comments reflectedan interest in making substantive changes in the role of the RAC but did not endorse its termination. Respondents voiced opposition to the concept of an OAC and stated that the proposed OAC functions could be accomplished by restructuring the RAC. Comments emphasized that the OAC would lack credibility that might impair the quality of public discussion if it was unable to attract and motivate the type of expertise and judgment needed for a comprehensive forum. Commentators expressed strong support for the role of the RAC as a forum for discussion of the ethical and societal issues raised by human gene transfer.

In response to public opinion and in keeping with the NIH Director's intent to increase the usefulness and productivity of public discussion of human gene transfer, the NIH Director published a revised proposal for Federal agency and public comment in the *Federal Register* on November 22, 1996 (61 FR 59726). This revised proposal retained the RAC, but modified its roles and responsibilities and reduced its membership from 25 members to 15. In doing so, the NIH Director acknowledged the public's view that the RAC has historical importance as a societal platform for discussion of scientific, ethical, and social issues involved in human gene transfer research.

The RAC discussed the NIH Director's revised proposal during its December 9, 1996, meeting, noted its acceptance of the overall structural changes proposed by the NIH Director, and concurred with reducing the membership. However, the RAC recommended that promulgation of these Proposed Actions (with the exception of reducing the committee membership) should be deferred pending further RAC discussion of minor procedural issues. The reduction in membership was incorporated as an amendment to the *NIH Guidelines* published in the *Federal Register* on January 31, 1997 (62 FR 4782). Issues that the RAC deemed worthy of further public discussion included: (1) the relationship between the RAC and GTPCs, (2) the timing of Institutional Biosafety Committee (IBC) and Institutional Review Board (IRB) approvals, and (3) the source of IBC approval.

In response to the RAC's request for continued discussion of the proposed changes, the NIH Director published a revised proposal in the *Federal Register* on February 14, 1997 (62 FR 7108) for Federal agency and public comment. The RAC continued its discussion of these changes during its March 6-7, 1997, meeting. After discussion, the committee recommended the following modifications regarding the relationship between the RAC and the GTPCs, and the timing and source of local institutional approvals: (1) The RAC should have primary responsibility for planning GTPC agendas, a member of the RAC should co-chair the GTPCs, and the RAC should summarize recommendations of the GTPCs in the form of a report to the NIH Director. The committee noted that this close relationship between the RAC and the GTPCs would not preclude other parties from suggesting GTPC topics, and that the GTPCs should be convened in consultation with the FDA. (2) To alleviate delays in the approval process at the

Federal level, local IBC and IRB approvals should be submitted prior to initiation of a clinical trial (rather than at the time of the protocol submission). (3) IBC approval should be submitted for each institution at which recombinant DNA material will be administered to human subjects (as opposed to each institution involved in the production of vectors for human application and each institution at which there is *ex vivo* transduction of recombinant material into target cells for human application).

These proposed changes reflect the adaptation of the role of the RAC in light of the present FDA safety and efficacy review process for human gene transfer protocols. Retention of the RAC review and

discussion of novel protocols reflects the continuing need for review and discussion of the scientific, ethical, and social aspects of this research.

V. Description of the Proposed Actions Under the *NIH Guidelines*

The *NIH Guidelines* provide a basic framework for safe and ethical conduct of recombinant DNA research. Recombinant DNA research involving human subjects should provide adequate assurance that the health and well-being of the subjects are protected. At the same time, the knowledge gained from individual recombinant DNA experiments should contribute to scientific research in general. Specifically, the design of such experiments should provide safeguards against vertical transmission of genetic changes from an individual to his/her offspring, or horizontal transmission of viral infection to other persons with whom the individual comes into contact. The *NIH Guidelines* define the responsibilities of the NIH Director, RAC, IBCs, and principal investigator(s), and they provide a framework for comprehensive risk assessment involving physical and biological containment practices and principles.

As knowledge increased, the NIH modified the requirements for submission, review, and approval for some categories of recombinant DNA experiments. These categories are those in which local institutional oversight proved capable of providing adequate assurance that the consequences of such experiments do not go beyond their purpose. Likewise, the FDA assesses whether additional information is needed for submission, review, and approval of IND applications; and the FDA has stringent general and specific procedures, standards, and requirements governing the entire process. These Proposed Actions to amend the *NIH Guidelines* are viewed as a natural extension of the previous actions taken by theNIH. As part of the continuing process to improve oversight of human gene transfer research, theNIH/ORDA and the FDA are working toward a simultaneous and unified submission format for human gene transfer protocols. In addition, the NIH and the FDA are looking at further defining and recognizing the roles of the IBC and the IRB in local oversight of human gene transfer protocols.

The *Coordinated Framework for Regulation of Biotechnology; Announcement of Policy and Notice for Public Comment* (*Coordinated Framework*) was published in the *Federal Register* on June 26, 1986 (51 FR 23302) to explain the proper allocation andcoordination of oversight responsibilities under the several relevant statutes and among the several relevant Federal agencies. The*Coordinated Framework* addressed who will have oversight authority in each instance. For research on foods, food additives, human drugs, medical devices and biologics, the *Coordinated Framework* specified that both the NIH and the FDA have jurisdiction. The *Coordinated Framework* stated that "to the extent possible, responsibility for a product use will lie with a single agency." (FR 51 23303)

In 1992, the Office of Science and Technology Policy issued a policy statement setting forth the proper basis for Federal agency exercise of oversight authority entitled:*Exercise of Federal Oversight Within Scope of Statutory Authority: Planned Introductions of Biotechnology Products into the Environment,* published in the *Federal Register* on February 27, 1992 (57 FR 6753). This scope document stated:

"…Agencies could develop categories of criteria for exercise of varying degrees of oversight options to correspond to degrees and types of risk. Some statutes arm that agency with an array of oversight instruments to deploy as the circumstances warrant. In such cases, agencies must decide not only whether or not to exercise oversight but also the appropriate level and type of oversight when it is exercised. Agencies could develop categories of criteria for exercise of varying degrees of oversight based on the degree of risk posed by an introduction, and the costs of oversight options. For example, oversight options include guidance on sound practices, simple notification to a local review committee, application for prior approval by a local review committee, notification to a Federal agency, considered deference to another agency already overseeing such introduction, or application for prior approval by a Federal agency.…" (57

FR 6759).

In keeping with the principles set forth in both the *Coordinated Framework* and the subsequent scope document, the Proposed Changes would eliminate the NIH duplication of the FDA statutory authority for oversight of safety and efficacy. In turn, the NIH would increase emphasis on issues of scientific design and potential ethical and social implications of human gene transfer research.

The review of human gene transfer clinical protocols considers multiple aspects: (1) safety, (2) scientific design, (3) efficacy, and (4) ethical and social implications of the proposed experiment. As with any proposal involving clinical research, the proposed benefit of the research must be carefully weighed against the potential risk to research subjects, health care workers, and the general public. Clearly, the FDA possesses both the expertise and statutory authority to assess safety and efficacy of human gene transfer clinical trials. In keeping with the spirit and intent of the *Coordinated Framework*, the RAC should logically provide oversight for those aspects of a protocol that are not the primary focus of the FDA review; namely, the social and ethical impacts of such research.

First, the RAC has been retained due to its historical importance in the field of human gene transfer (rather than being replaced by a different advisory committee). The roles and responsibilities of the RAC have been modified to increase its effectiveness in carrying out its responsibilities. The RAC will continue to set the ethical framework for the conduct of human gene transfer experiments through the development and maintenance of appropriate guidance documents developed in conjunction with other Federal agencies and the public. The RAC will ensure public access to and scrutiny of human gene transfer experiments and will use its unique role to serve as an educational forum for human gene transfer technologies, developments in biomedical research, and their potential impact on research subjects and the public.

Second, the NIH will relinquish general approval responsibilities to the FDA, which has statutory authority for such approval. The Consolidated Review process, adopted by the NIH Director on April 17, 1995, was a combined effort by the FDA and the NIH to streamline the approval process of all human gene transfer experiments. Under these new Proposed Actions, general approval authority will rest with the FDA, eliminating overlapping approval procedures.

Third, the NIH has instituted regularly convened GTPCs, co-chaired by a member of the RAC. The NIH convened the first GTPC on September 11, 1997. To ensure a close working relationship between the RAC and the GTPCs, the RAC will have primary responsibility for planning GTPC agendas, and a RAC member will co-chair each GTPC. Further, these conferences will be held in conjunction with the RAC meetings, when appropriate, and all RAC members will be invited to attend the GTPCs.

Fourth, the NIH will maintain and improve public access to human gene transfer information. The ORDA data management process will provide administrative details of protocol registration, annual status reports, and risk assessments. This database will improve public access to human gene transfer clinical trial information, including adverse event reporting.

Through these actions, the NIH will maintain appropriate scientific and ethical oversight of recombinant DNA activities and increase the effectiveness of public discussion. Moreover, these actions will ensure the efficient use of Federal resources.

VI. Description of the Alternatives

One alternative to the Proposed Actions is the no action alternative, which would retain the currently practiced polices and procedures under the Consolidated Review. This option is not viable for a number of

reasons. The current Consolidated Review provisions hinder efficient review at the Federal level because of duplicate review by the NIH and the FDA. Such duplication of effort is not necessary to safeguard research subjects, researchers, or the public. The Proposed Actions have been extensively considered, and subsequently accepted, by all interested parties. Rejecting the ProposedActions in favor of no action would significantly diminish the efforts over the past four years and would require cessation of some actions already implemented.

A second alternative is to revert to the Proposed Actions of July 8, 1996. That proposal abolished the RAC in favor of a new NIH advisory committee with a small number of members. This alternative is not viable because it was rejected after NIH consultation with the RAC and with input from the public.

A third alternative is some different combination of the Proposed Actions. Any such combination would be undesirable, because it would not be the product of the extensive public discussion that led to the Proposed Actions under the *NIH Guidelines*.

As discussed below, it appears that the environmental impacts of all these alternatives are essentially the same as the limited environmental impact of the Proposed Actions, because the coordinated review by the FDA and the IBC of the potential environmental effects of the proposed research is unchanged.

VII. Environmental Impact of the Proposed Actions Under the *NIH Guidelines*

These Proposed Actions pertain only to changes in the administration of scientific research (rather than to physical changes, e.g., constructing a building), and there is no significant change in the thoroughness of the review of human gene transfer experiments. Therefore, there is no significant impact on the human environment, as defined by the Council on Environmental Quality in 40 CFR Part 1508. However, in order to comply fully with provisions in 40 CFR Part 1508 regarding effects on the human environment, this document assesses the impact of these Proposed Actions.

A. Impact of Promulgating the Proposed Actions Under the *NIH Guidelines*

A central question regarding the impact of the Proposed Actions is whether the thoroughness of the current review of potential environmental effects will be compromised. Specifically, will this change in the review process increase the risk of harm to the human environment? There are two basic concerns that should be considered in addressing this question: (1) the risk of harming the patient or researchers directly involved in conducting the experiment, and (2) the risk of harming others not directly involved.

The possibility that this change will increase the risk of harm to persons directly involved in the experiment is sufficiently addressed by the FDA regulations and by provisions of 45 CFR Part 46, as amended, *Protection of Human Subjects*, as administered by the Office for Protection from Research Risks (OPRR). Section 46.101 applies to all human subject research funded or conducted by the 17 Federal departments and agencies that have promulgated the policy. The same section states "Research that is neither conducted nor supported by one of these agencies, but is subject to regulation . . . must be reviewed and approved . . . by an IRB that operates in accordance with the pertinent requirements of this policy." In §46.102, IND requirements administered by the FDA are cited as a specific example of such regulation.

Because of this applicable language, the scope of the FDA review and approval process includes all human gene transfer clinical trials, regardless of who funds the trial or who conducts it. In 21CFR § 312.22(a), these IND requirements specifically state that the "FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects . . . ." Under provisions of 21 CFR § 312.42, the FDA has authority to impose a clinical hold on any experiment for a number of

reasons, including the possibility that the safety of the human subjects would be at risk. In 21CFR § 56.111, there are specific criteria the IRB must use to minimize risks to subjects before approving the research. Suspension or termination of IRB approval of the research is governed by 21 CFR § 56.113. The FDA retains the authority to ensure that the subjects of the research are protected and that other IND requirements are met (21 CFR Part 312, Subpart C). Because human gene transfer protocols will remain within the scope of the regulations providing for the protection of human subjects with review and approval by the IRB and with compliance under the purview of the FDA, or the OPRR if the research is funded by the NIH, there will continue to be stringent review mechanisms to ensure that human subjects are protected from any significant risk of harm.

The possibility that this change will increase the risk of harming others *not* directly involved in the experiment, i.e., the larger public, is sufficiently addressed by the combined oversight of the FDA and the local IBC. First, the FDA's regulations governing the review and approval of human gene transfer protocols provide for an assessment of the environmental effects under 21CFR § 312.23 (a) (7) (iv) (e).INDs are normally categorically excluded from the requirement to prepare an EA or an environmental impact statement under 21 CFR § 25.31 (e). However, as required under 40CFR § 1508.4 and 21 CFR § 25.21, the FDA will require at least an EA for any specific action that ordinarily would be categorically excluded if extraordinary circumstances indicate that the specific proposed action may significantly affect the quality of the human environment. This requirement to prepare an EA in extraordinary circumstances would apply to any human gene transfer experiment, or any other action, "for which available data establish that, at the expected level of exposure, there is the potential for serious harm to the environment."

Section IV-B-2 of the *NIH Guidelines* requires creation of an IBC and sets forth the functions and responsibilities of this body. These functions include assessing risk, setting containment levels, and adopting emergency plans prior to approval of the research by the IBC. It is important to note that IBC approval is still required prior to initiation of any human gene transfer experiment conducted at, or in collaboration with, an institution that receives NIH funding for recombinant DNA research, even with the NIH relinquishing its authority for general approval of individual human gene transfer experiments. These IBC safeguards in Section IV-B-2, along with the FDA's IND review and IRB review, will help ensure that neither human subjects nor the human environment will be significantly affected by the cessation of the NIH's authority to approve human gene transfer protocols.

As noted earlier, the FDA's approval authority for INDs applies to the human gene transfer protocols currently subject to review and approval by the NIH. In a FDA agency statement entitled, *Application of Current Statutory Authorities to Human Somatic Cell Therapy Products and Gene Therapy Products* (*Federal Register* on October 14, 1993, 58 FR 53248), the FDA defined human gene transfer products as "products containing genetic material administered to modify or manipulate the expression of genetic material or to alter the biological properties of living cells" (58 FR 53249). The NIH's proposed action includes these types of products. The FDA's statement notes specifically that, "In accordance with the statutory provisions governing biological products and drugs, a . . . gene therapy product must be the subject of an IND in compliance with part 312 or of an approved PLA (Product License Application). . . ."(58 FR 53250).

Other impacts of the Proposed Actions affect the work of both the NIH and the FDA. These Proposed Actions alleviate the workload for the NIH due to the modifications of the RAC's roles and responsibilities. The NIH will be able to redirect Federal resources toward other tasks in its primary areas of responsibility. For example, under the revised proposal, the RAC is retained to discuss significant issues and policies in recombinant DNA research, such as scientific concerns, ethical conduct, and societal implications. GTPCs will convene public forums to discuss significant issues arising from this research. Additionally, the ORDA will be able to better facilitate public access to information relevant to human gene transfer research.

Recognizing that the FDA has general regulatory authority over all human gene transfer clinical trials, eliminating the required duplicate submissions will likely reduce the time for the FDA approvals. Therefore, implementation of the Proposed Actions will facilitate the efforts by both agencies to concentrate on their primary responsibilities. This concentrated effort will produce a more efficient use of Federal resources while maintaining the necessary oversight of human gene transfer experiments.

B. Assessment of Probabilities of Adverse Effects of Promulgating the Proposed Actions Under the *NIH Guidelines*

The Proposed Actions address the issues and concerns about potential adverse effects that were raised in the previous 18 months in which the Proposed Actions were developed and refined. The main concerns of the public and scientific communities pertained to social and ethical issues, public accountability anddiscussion, and public access to information relating to human gene transfer clinical trials. In response, the NIH Director provided effective mechanisms by which each of these concerns can be adequately addressed.

In addition to these general concerns, there are specific concerns regarding potential human environmental effects that should be addressed. These specific public health concerns are contained in the *NIH Guidelines*, Appendix M-II-B-4, entitled "Public Health Considerations." They are: "Appendix M-II-B-4-a. On what basis are potential public health benefits or hazards postulated?; Appendix M-II-B-4-b. Is there a significant possibility that the added DNA will spread from the patient to other persons or to the environment?; Appendix M-II-B-4-c. What precautions will be taken against such spread (e.g., patients sharing a room, health-care workers, or family members)?; Appendix M-II-B-4-d. What measures will be undertaken to mitigate the risks, if any, to public health?; Appendix M-II-B-4-e. In light of possible risks to offspring, including vertical transmission, will birth control measures be recommended to patients? Are such concerns applicable to health care personnel?"

These specific public health concerns are satisfied by the fact that these issues will be addressed by the IRBs and the IBCs, as well as through the FDA's detailed procedures governing INDs set forth in 21 CFR § 312.23(a). These regulations state that every IND must contain "a commitment to conduct the investigation in accordance with all other applicable regulatory requirements." Additionally, both the FDA and the NIH are covered by the same requirements of HHS General Administration Manual Chapter 30-60, which states that HHS components "must determine that the action taken by a program would never significantly affect the quality of the human environment."

The possibility of adverse effects due to promulgating the Proposed Actions was analyzed and evaluated in the development of the proposal. After careful consideration, the NIH provided responses to address the main concerns expressed by the written comments as well as to provide comprehensive coverage of factors involved in human gene transfer research. Under the new process, the FDA will regulate each protocol and the IRB and the IBC will be involved as discussed above. The RAC will focus on the ethical and societal issues of human gene transfer. As a result, the concerns of both the individual and society at-large are sufficiently addressed. Therefore, the probability of any adverse effects on either human subjects or the human environment is negligible.

C. Experiments Impacted by the Proposed Actions under the *NIH Guidelines*

Under the Consolidated Review process, all human gene transfer clinical trials conducted at an institution that receives NIH funding for recombinant DNA research, or in collaboration with an institution that receives NIH funding for recombinant DNA research, are required to be submitted to the NIH and

aresubject to potential review and approval by the RAC and the NIH Director. In turn, these same protocols must be reviewed and approved by the FDA under 21 CFR Part 312 pertaining to INDs. The Proposed Actions put forth by the NIH Director in the *Federal Register* announcements of July 8, 1996, November 22, 1996, and February 14, 1997, would terminate the NIH approval procedures for such experiments, eliminating duplication of effort between the NIH and the FDA.

The Proposed Actions will result in similar and consistent requirements for human gene transfer experiments developed by academic institutions and by private industry. Federally funded experiments no longer will be governed by approval procedures and restrictions imposed by two different agencies; instead, the FDA will provide uniform oversight of human gene transfer clinical trials. The FDA will have primary responsibility for evaluating safety and efficacy of individual human gene transfer protocols to ensure compliance with established standards. The IRB and the IBC will retain their current roles and responsibilities in the evaluation process. Additionally, the type of experiments that may be proposed is not changed or restricted. Therefore, review of human gene transfer experiments will become no less rigorous in terms of protecting human subjects and the human environment.

D. Benefits of the Proposed Actions Carried Out Under the *NIH Guidelines*

Implementation of a single Federal approval process will decrease the burden for researchers and will expedite the approval of relevant INDs and ensure efficient use of fiscal resources.

Each human gene transfer experiment will continue to be registered with the NIH, but for a different purpose than to obtain approval. The RAC will be able to review and discuss any protocols it deems as "novel," e.g., those that propose new applications, use new delivery systems, involve new patient populations, or raise ethical concerns. Upon completion of the public discussion, the RAC may make recommendations concerning issues raised by these protocols to the NIH Director, the Principal Investigator, sponsoring institution, and other HHS components as appropriate. Registration will be used to track the progression of human gene transfer research. Additionally, registration will focus attention on public education and the debate of broader scientific and societal issues relevant to human gene transfer research. As a result, the public will be able to keep abreast of innovative and novel applications of human gene transfer research and closely monitor adverse events. Therefore, the modifications to the RAC's role and responsibility will further the purpose and goals of both agencies.

The Proposed Actions will benefit both the public and the Federal government. For example, the Proposed Actions define the venue and responsibility of the NIH. By specifying boundaries, the Proposed Actions clarify the roles of the RAC and the NIH so both the FDA and the NIH can focus attention on completing their primary duties. Each agency will specialize in a particular aspect of human gene transfer research, rather than using the current dual approval process that results in overlapping responsibilities. The NIH will refocus its efforts on the consideration of relevant policy issues and dissemination of public information, while the FDA will administer approval of specific protocols based on safety and the subject's welfare. These clarifications and limitations allow both agencies to concentrate on specified goals in the field of human gene transfer research and to accomplish these goals more efficiently.

The NIH and the public will benefit because the Proposed Actions encourage public discussion of scientific, ethical, and legal issues surrounding human gene transfer in public forums such as the GTPCs. The GTPCs will represent different views, address various concerns, and ensure quality discussion that encompasses a broad spectrum of issues relevant to human gene transfer research. This early public discussion of scientific and societal issues, in advance of human applications, holds the promise of benefiting all parties -- the public, academia, the NIH, the FDA, and industry. Focused discussion in these forums will promote consideration of issues that are beyond the safety and efficacy of individual

experiments, and will provide additional perspectives in the submission and consideration of individual INDs.

Moreover, the NIH Director's proposal to develop and maintain a publicly accessible human gene transfer database within the ORDA provides the public with another tool to review human gene transfer research procedures, methodologies, and results. Public access to this database will provide useful information for the scientific community, ensuring minimal duplication of research effort and identifying gaps in knowledge. Researchers will be required to register experiments with the NIH and to provide additional information pertaining to the protocol, adverse effects, and follow-up data. This database will be a vital tool for ensuring public confidence, providing patient access to relevant clinical trials, and expanding the public's understanding of human gene transfer research and its potential benefits.

An additional benefit of the Proposed Actions is that they are consistent with the goals and actions stated in the Vice President's National Performance Review and the Government Performance and Review Act. The Proposed Actions achieve the overall goals of these two initiatives designed to reinvent government: improve interagency coordination, reduce duplication of efforts, and alleviate bureaucratic procedures. The Proposed Actions promote efficiency by eliminating duplication of efforts by the NIH and the FDA in the review of human gene transfer research.

In summary, the interests of both the public and the government are served through the promulgation of the Proposed Actions. The public benefits by the NIH maintaining the accountability of the scientific community throughpreservation of the RAC, facilitating early public discussion of significant scientific and societal issues by the RAC and the GTPCs, and improving public access to human gene transfer data. The scientific research community and biotechnology industry benefit from the expedited review ofIND applications. The government gains by eliminating duplication of effort, reducing the workload of two major Federal agencies, and allowing increased concentration on their respective agency goals and responsibilities.

VIII. Finding of No Significant Impact

These Proposed Actions are limited in scope and are administrative in nature. Although the NIH administrative role in approving individual human gene transfer protocols is eliminated, this change has no effect on the FDA approval process which, together with theIRB and the IBC reviews, adequately protects subjects, researchers, and the human environment. As a result, there is a negligible impact on the overall integrity of the process for reviewing and approving individual human gene transfer experiments. At the same time, the Proposed Actions reinforce the public health mission of each agency by reducing duplication of effort and enhancing service to the public.

After due consideration of all the relevant issues, there is a finding of no significant impact on the environment.

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