DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Office of Recombinant DNA Activities; Recombinant DNA Research: Proposed Actions Under the NIH Guidelines

AGENCY: National Institutes of Health (NIH), PHS, DHHS.

ACTION: Notice of proposed actions under the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines).

SUMMARY: The purpose of this document is to inform the public of proposed changes to the NIH Guidelines related to the reporting of serious adverse events involving human gene transfer research. This notice describes a proposed action to amend the NIH Guidelines regarding the reporting and public disclosure of serious adverse events.

DATES: The public is encouraged to submit written comments on these proposed changes to the NIH Office of Recombinant DNA Activities (ORDA). Written comments may be submitted to NIH/ORDA in paper or electronic form. Written comments received by December 3, 1999, will be reproduced and distributed to the RAC for consideration at its December 8–10, 1999, meeting.

All comments received in response to this notice will be considered by the NIH and will be available for public inspection in the NIH/ORDA office weekdays between the hours of 8:30 a.m. and 5 p.m.

FOR FURTHER INFORMATION CONTACT: If you have questions, or require additional information about these proposed changes to the NIH Guidelines, please contact the Office of Recombinant DNA Activities (ORDA) by e-mail at: ci4e@nih.gov, or telephone at: 301–496–9838. Written comments on these proposed changes to the NIH Guidelines can be submitted by e-mail to: ci4e@nih.gov, fax to: 301–496–9839, or mail to: the Office of Recombinant DNA Activities, National Institutes of Health, MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010.

For additional information about the December 8–10, 1999, RAC meeting at which these proposed changes will be deliberated, please visit the NIH/ORDA web site at: http://www.nih.gov/od/orda/.

SUPPLEMENTARY INFORMATION: Appendix M–VII–C of the NIH Guidelines requires Principal Investigators (or their designated sponsors) to report serious adverse events immediately to the local Institutional Review Board (IRB), Institutional Biosafety Committee (IBC), Office for Protection from Research Risks (OPRR) (if applicable), NIH/ORDA, and Food and Drug Administration (FDA).

All non-NIH funded projects involving recombinant DNA techniques conducted at or sponsored by an institution that receives NIH support for projects involving such techniques must comply with the NIH Guidelines. Noncompliance may result in: (i) Suspension, limitation, or termination of NIH funds for recombinant DNA research at the institution, or (ii) a requirement for prior NIH approval of any or all recombinant DNA projects at the institution.

All gene transfer clinical studies are subject to FDA regulations found in volume 21 of the Code of Federal Regulations (CFR), including specific requirements at 21 CFR 312.32 related to adverse events.

The immediate reporting of serious adverse events to NIH/ORDA by investigators allows rapid notification of the RAC. This, in turn, allows notification, as appropriate, of other IBCs, IRBs, and Principal Investigators in the field. Immediate reporting also provides a unique mechanism for early recognition of trends in the occurrence of serious adverse events that may raise significant implications for the safety of patients enrolled in similar human gene transfer studies. For example, there have been several instances in which public RAC discussion of serious adverse events has resulted in important changes in the design of vectors for gene delivery. When deemed appropriate, NIH/ORDA will initiate additional data collection for a comprehensive and public review by the RAC and ad hoc experts. This process fosters broad public awareness of issues and developments in human gene transfer research. The comprehensive public review of data by the RAC is a critical component of Federal oversight of gene transfer research.

Recently some investigators and sponsors have begun to designate human gene transfer protocols or serious adverse event reports confidential, thereby precluding public RAC review. Out of concern about this development, the NIH requested that the RAC consider whether the requirement for serious adverse event reporting as set forth in the NIH Guidelines needed to be clarified.

During the September 2–3, 1999, meeting, the RAC developed the following consensus statement with regard to serious adverse event reporting to NIH/ORDA and the RAC: ''Adverse event reports shall not be designated as confidential, either in whole or in part. Adverse event reports are essential to decision-making by IBCs, IRBs, and potential subjects of gene transfer research in humans. The public disclosure of adverse events [in human gene transfer research] is also essential to public understanding and evaluation of gene transfer in humans. Adverse event reports must be made available for public discussion [by the RAC] without the inclusion of proprietary or trade secret information.''

Some investigators have not complied with the NIH Guidelines requirement to report serious adverse events immediately to the NIH/ORDA. While the NIH Guidelines are clear on this matter, the NIH is proposing to amend the NIH Guidelines to restate the requirements for serious adverse event reporting and to include: (1) A definition of serious adverse events and a stipulation of the time-frame in which they are to be reported in writing (adapted from 21 CFR 312.32 IND Safety Reports); (2) a mandate that serious adverse event reports must not contain any trade secret or commercial or financial information that is privileged or confidential and that all information submitted in accordance with Appendix M–VII–C will be considered public unless NIH ORDA determines that there are exceptional circumstances; and (3) a directive that serious adverse event reports submitted to ORDA be stripped of individually-identifiable patient information.

Proposed Amendments to the NIH Guidelines

A new Section I–E–7 is added to read:

''Section I–E–7. A ''serious adverse event'' is defined as any expected or unexpected adverse event, related or unrelated to the intervention, occurring at any dose that results in any of the following outcomes; death, a life-threatening event, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization also may be considered a serious adverse event when, based upon appropriate medical judgement, they may jeopardize the human gene transfer research subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.''

Appendix M, Points To Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules Into One or More Human Subjects (Points To Consider)

Appendix M–VII–C, Serious Adverse Events, is proposed to read:

''Appendix M–VII–C–1, Serious Adverse Event Reporting

''Principal Investigators who have received authorization from FDA to initiate a human gene transfer protocol must report immediately in writing any serious adverse event (as defined in Section I–E–7) to the local Institutional Review Board, Institutional Biosafety Committee, Office for Protection from Research Risks (if applicable), NIH/ORDA, and FDA.

''Serious adverse event reports must not contain any trade secret or commercial or financial information that is privileged or confidential as defined under the Freedom of Information Act, 5 U.S.C. 552; therefore, unless NIH/ORDA determines that there are exceptional circumstances, all information submitted in accordance with Appendix M–VII–C will be considered public.

''Reports of serious adverse events may be submitted by e-mail to: ci4e@nih.gov, fax to: 301–496–9839, or by mail to: the Office of Recombinant DNA Activities, National Institutes of Health, MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010.

Appendix M–VII–C–2, Serious Adverse Event Reporting: Content and Format

''Reports of serious adverse events must follow the format provided in the Adverse Event Reporting Form available on NIH/ORDA's web site at: http://www.nih.gov/od/orda/. The serious adverse event report must include, but need not be limited to: (1) The date of the event; (2) a complete description of the event; (3) relevant clinical observations; (4) relevant clinical history; (5) relevant tests that were or are planned to be conducted; (6) the suspected cause of the event; (7) gene delivery method; (8) vector type, *e.g.*, adenovirus; (9) vector subtype, *e.g.*, type 5, relevant deletions; (10) dosing schedule; (11) route of administration; (12) clinical site; (13) principal investigator(s); (14) NIH Protocol number; and (15) Investigational New Drug (IND) number.

''Serious adverse event reports should be stripped of individually-identifiable patient information. Examples of such information include, but are not limited to, the patient's name, address, contact information, social security number, date of birth.

''Appendix M–VII–C–3, Time-Frames for Serious Adverse Event Reporting: Initial and Follow-Up Reports

''Immediate reporting of serious adverse events is essential for the early identification of acute events related to a gene transfer procedure, as well as the identification of patterns that may signal potential safety concerns. For the purposes of the NIH Guidelines, 'immediate' written reporting of all serious adverse events is to occur as soon as possible but no later than 15 calendar days after such an event has occurred. This applies to all serious adverse events, related or unrelated to gene transfer, which occur during the course of the clinical trial.

''Relevant additional clinical and laboratory data may become available following the initial serious adverse event report. The Principal Investigator(s) must provide any relevant follow-up information to a serious adverse event report within 15 calendar days of receipt of the relevant information. In addition, if a serious adverse event occurs after the end of a clinical trial, and is determined to be related to gene transfer, that event shall be reported by the Principal Investigator within 15 calendar days of the determination.''

OMB's ''Mandatory Information Requirements for Federal Assistance Program Announcements'' (45 FR 39592) requires a statement concerning the official government programs contained in the Catalog of Federal Domestic Assistance. Normally, NIH lists in its announcements the number and title of affected individual programs for the guidance of the public. Because the guidance in this notice covers virtually every NIH and Federal research program in which recombinant DNA techniques could be used, it has been determined not to be cost effective or in the public interest to attempt to list these programs. Such a list would likely require several additional pages. In addition, NIH could not be certain that every Federal program would be included as many Federal agencies, as well as private organizations, both national and international, have elected to follow the NIH Guidelines. In lieu of the individual program listing, NIH invites readers to direct questions to the information address above about whether individual programs listed in the Catalog of Federal Domestic Assistance are affected.

Dated: November 16, 1999.

Lana Skirboll,

Associate Director for Science Policy, National Institutes of Health.

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DEPARTMENT OF THE INTERIOR

Bureau of Land Management

[CA–066–99–1990–00; CACA–20139 and CACA–22901]

Notice of Availability of Supplemental Environmental Impact Statement and Preferred Action for the Proposed Sand and Gravel Mining Operation, Los Angeles County, CA

AGENCY: Bureau of Land Management, Department of the Interior, Palm Springs-South Coast Field Office, Desert District, California.

ACTION: Notice of availability of supplemental environmental impact statement and identification of preferred action.

SUMMARY: In compliance with the National Environmental Policy Act (NEPA) of 1969 and 40 CFR 1503.1(a), notice is hereby given that the Bureau of Land Management (BLM) has prepared a supplement to the Draft Environmental Impact Statement (EIS). This supplement to the Draft EIS addresses a new proposal by Transit Mixed Concrete Company to transport mine material by a conveyor belt system rather than open trucks as proposed in the original draft EIS. The supplement will provide; further analysis of the potential air quality impacts. In addition the supplement identifies the BLM's preferred action. Interested citizens are invited to review the Supplement and submit comments. Copies of the Supplement may be obtained by telephoning or writing to the contact person listed below. Public reading copies of the Supplement are available at the following County of Los Angeles public libraries: Canyon County Library, 18536 Soledad Canyon Road, Santa Clarita, CA 91351; Newhall Library, 22704 W. Ninth Street, Santa Clarita, CA 91321; Valencia Library, 23743 W. Valencia Boulevard, Santa Clarita, CA 91355.

DATES: Comments must be received in writing to the BLM no later than January 10, 2000.

ADDRESSES: Written comments shall be mailed to the following address: Mr. James G. Kenna, Field Manager, Bureau of Land Management, Palm Springs-South Coast Field Office, 690 W. Garnet Avenue, PO Box 1260, North Palm Springs, California, 92258. Comments may also be submitted by electronic mail (E-mail) to the following address: emisquez@ca.blm.gov. The response to comments will be provided in the Final EIS.

FOR FURTHER INFORMATION CONTACT: Ms. Elena Misquez, BLM, Palm Springs-South Coast Field Office, PO Box 1260, North Palm Springs, CA 92258, telephone 760–251–4804.

Dated: November 12, 1999.

Carole Levitzky,

Assistant District Manager, External Affairs.

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