DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Recombinant DNA Research: Proposed Actions Under the 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: This notice sets forth proposed actions to be taken under the NIH Guidelines for Research Involving Recombinant DNA Molecules (59 FR 34496, amended 59 FR 40170, 60 FR 20726, 61 FR 1482, 61 FR 10004, 62 FR 4782, 62 FR 53335, 62 FR 56196, 62 FR 59032). Interested parties are invited to submit comments concerning these proposals. These proposals will be considered by the Recombinant DNA Advisory Committee (RAC) at its meeting on December 15–16, 1997, along with the proposed actions published in the **Federal Register** on October 16, 1997 (62 FR 53908). After consideration of these proposals and comments by the RAC, the NIH Director will issue decisions in accordance with the NIH Guidelines.

DATES: Interested parties are invited to submit comments concerning the proposed actions. Comments received by December 8, 1997, will be reproduced and distributed to the RAC for consideration at its December 15–16, 1997, meeting. After consideration of this proposal and comments by the RAC, the NIH Director will issue decisions in accordance with the NIH Guidelines.

ADDRESSES: Written comments and recommendations should be submitted to Debra Knorr, Office of Recombinant DNA Activities, National Institutes of Health, MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, Phone 301–496–9838, FAX 301–496–9839.

All comments received in response to this notice will be considered and will be available for public inspection in the above office on weekdays between the hours of 8:30 a.m. and 5:00 p.m.

FOR FURTHER INFORMATION CONTACT: Background documentation and additional information can be obtained from the Office of Recombinant DNA Activities, National Institutes of Health, MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, Phone 301–496–9838, FAX 301–496–9839. The Office of Recombinant DNA Activities web site is located at http://www.nih.gov/od/orda for further information about the office.

I. Proposed Actions Regarding Amendments to the NIH Guidelines

The NIH will consider the following actions under the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines):

I–A. Amendment to Appendix M–I, Submission Requirements—Human Gene Transfer Experiments, Under the NIH Guidelines Regarding Deadline for Submission for RAC Review

On November 12, 1997, Dr. Scott McIvor, a member of the Recombinant DNA Advisory Committee (RAC), requested a proposed action regarding the deadline for submission of human gene transfer protocols that will require public discussion at the RAC meetings.

To give the RAC sufficient time to review the protocols and the investigators to respond to primary reviewer's written comments, Appendix M–I, Submission Requirements—Human Gene Transfer Experiments, of the NIH Guidelines, is proposed to be amended to include a statement regarding the submission deadline. Submission material will be accepted by NIH/ORDA at any time. However, if a protocol is recommended for full RAC review, the submission material must be received in NIH/ORDA a minimum of eight weeks prior to the next scheduled RAC meeting.

Appendix M–I is proposed to read:

''Appendix M–I. Submission Requirements—Human Gene Transfer Experiments

''Investigators must submit the following material to the Office of Recombinant DNA Activities, National Institutes of Health/MSC 7010, 6000 Executive Boulevard, Suite 302, Bethesda, Maryland 20892–7010, (301) 496–9838 (see exemption in Appendix M–VIII–A, Footnotes of Appendix M). Proposals shall be submitted to NIH/ORDA in the following order: (1) Scientific abstract; (2) non-technical abstract; (3) Institutional Biosafety Committee and Institutional Review Board approvals and their deliberations pertaining to your protocol (Instutitional Biosafety Committee approval must be obtained from 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 DNA material into target cells for human application)); (4) Responses to Appendix M–II through M–V. Description of the Proposal, Informed Consent, Privacy and Confidentiality, and Special Issues (the pertinent responses can be provided in the protocol or as an appendix to the protocol); (5) clinical protocol (as approved by the local Institutional Biosafety Committee and Institutional Review Board); (6) Informed Consent Document—approved by the Institutional Review Board (see Appendix M–III, Informed Consent); (7) appendices (including tables, figures, and manuscripts); and (8) curricula vitae—2 pages for each key professional person in biographical sketch format. Investigational New Drug (IND) applications shall be submitted to FDA in the format described in 21 CFR, Chapter I, Subchapter D, Part 312, Subpart B, Section 23, IND Content and Format. Submissions to FDA should be sent to the Division of Congressional and Public Affairs, Document Control Center, HFM–99, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Rockville, Maryland 20852–1448.

''**Note:** Submission material will be accepted by NIH/ORDA at any time. However, if a protocol is recommended for full RAC review, the submission material must be received in NIH/ORDA a minimum of eight weeks prior to the next scheduled RAC meeting.''

I–B. Amendment to Appendix K, Physical Containment for Large Scale Uses of Organisms Containing Recombinant DNA Molecules, of the NIH Guidelines

In a letter dated November 5, 1997, Gerard J. McGarrity, Ph.D., Senior Vice President for Development, Genetic Therapy, Inc., Gaithersburg, Maryland, requested amendments to Appendix K, Physical Containment for Large Scale of Uses of Organisms Containing Recombinant DNA Molecules, of the NIH Guidelines to clarify the containment requirements for large scale production of viral vectors for gene therapy. The letter states that:

''The purpose of this correspondence is to point out a section of Appendix K of the NIH Guidelines (January 1997) that requires clarification for large scale production of viral vectors for gene therapy.

''Appendix K specifies containment guidelines for research or production material that exceed 10 liters in volume. Each of the large scale (LS) biosafety levels (BL): Good Large Scale Production (GLSP), BL1/LS (Appendix K–III–C), BL2/LS (Appendix K–IV–C) and BL3/LS (Appendix K–V–C) specify the requirements that:

'Culture fluids (except as allowed by Appendix K–III–D, K–IV–D, K–V–D) shall not be removed from a closed system or other primary containment equipment unless the viable organisms containing recombinant DNA molecules have been inactivated by a validated inactivation procedure.'

''Related language addresses the primary containment equipment:

'A closed system or other primary containment equipment that has contained viable organisms containing recombinant DNA molecules shall not be opened for maintenance or other purposes unless it has been sterilized by a validated sterilization procedure.' (Sections K–III–F, K–IV–F and K–V–F)

''As its title (Physical Containment for Large Scale Uses of Organisms Containing

Recombinant DNA Molecules) indicates. Appendix K was written to deal with prokaryotic and eukaryotic cells that elaborate proteins expressed by recombinant DNA molecules. It was not intended for the production of viral vectors used in gene therapy. If fact, adherence to sections K–III–C, K–IV–C, or K–V–C is incompatible with the production and harvest of viral vectors in volumes larger than 10 liters as active viral vectors must be removed from the equipment. Clearly, this was not the purpose of Appendix K.

''Several possible solutions exist. First, Section III–D–6 of the Guidelines, 'Experiments Involving More Than 10 Liters Of Culture,' states:

'The appropriate containment will be decided by the Institutional Biosafety Committee. Where appropriate, Appendix K, Physical Containment for Large Scale Uses of Organisms Containing Recombinant DNA Molecules, shall be used.'

''We interpret this to mean that for production of viral vectors, the IBC has the authority to establish the specifics of large scale containment, using the principles described in Appendix K. For harvesting of supernatant fluids that contain the viral vector product, the IBC can establish practices and facilities which are consistent with the objectives and spirit of the NIH Guidelines.

''In this regard, Genetic Therapy, Inc., has adhered to Section III–D–6 in the establishment of facilities and practices for large scale production of retroviral vectors to the extent that Sections can be applied to viral vectors. These have included the practices for the appropriate large scale biosafety level except for the requirement to inactivate the culture fluids and to sterilize the primary containment equipment prior to opening the primary containment equipment and removing the culture fluids. These practices have been approved by our IBC.

''A second possible solution is to limit volumes to less than 10 liters. However, this will be impractical for commercial purposes. Third, the Guidelines can be modified to address the requirements for large scale production of viral vectors for gene therapy.

''For the longer term, we believe it is most appropriate to revise the relevant portions of Appendix K to enable application of large scale to viral vectors. We request that RAC address this issue and propose the following language be added to the end of Section K–III–C, K–IV–C and K–V–C of Appendix K:

'Culture fluids that contain viable organisms or viral vectors intended as final product may be removed from the primary containment equipment by way of closed systems for sample analysis, further processing or final fill.'

''We propose the following language be added to the end of the first sentence of Sections K–III–F, K–IV–F and K–V–F:

'* * * except when the culture fluids contain viable organisms or vectors intended as final product as described in Section K–III–C (or K–IV–C or K–V–C respectively) above.'

''We believe these additions maintain the original concept of Appendix K while addressing the needs of specific product types.''

Appendix K–III–C is proposed to read:

''Appendix K–III. Biosafety Level (BL1)—Large Scale

''Appendix K–III–C. Culture fluids (except as allowed in Appendix K–III–D) shall not be removed from a closed system or other primary containment equipment unless the viable organisms containing recombinant DNA molecules have been inactivated by a validated inactivation procedure. A validated inactivation procedure is one which has been demonstrated to be effective using the organism that will serve as the host for propagating the recombinant DNA molecules. Culture fluids that contain viable organisms or viral vectors intended as final product may be removed from the primary containment equipment by way of closed systems for sample analysis, further processing or final fill.''

Appendix K–III–F is proposed to read:

''Appendix K–III–F. A closed system or other primary containment equipment that has contained viable organisms containing recombinant DNA molecules shall not be opened for maintenance or other purpose unless it has been sterilized by a validated sterilization procedure except when the culture fluids contain viable organisms or vectors intended as final product as described in Section K–III–C above. A validated sterilization procedure is one which has been demonstrated to be effective using the organism that will serve as the host for propagating the recombinant DNA molecules.''

Appendix K–IV–C is proposed to read:

''Appendix K–IV. Biosafety Level 2 (BL2)—Large Scale

''Appendix K–IV–C. Culture fluids (except as allowed in Appendix K–IV–D) shall not be removed from a closed system or other primary containment equipment unless the viable organisms containing recombinant DNA molecules have been inactivated by a validated inactivation procedure. A validated inactivation procedure is one which has been demonstrated to be effective using the organism that will serve as the host for propagating the recombinant DNA molecules. Culture fluids that contain viable organisms or viral vectors intended as final product may be removed from the primary containment equipment by way of closed systems for sample analysis, further processing or final fill.''

Appendix K–IV–F is proposed to read:

''Appendix K–IV–F. A closed system or other primary containment equipment that has contained viable organisms containing recombinant DNA molecules shall not be opened for maintenance or other purposes unless it has been sterilized by a validated sterilization procedure except when the culture fluids contain viable organisms or vectors intended as final product as described in Section K–IV–C above. A validated sterilization procedure is one which has been demonstrated to be effective using the organisms that will serve as the host for propagating the recombinant DNA molecules.''

Appendix K–V–C is proposed to read:

''Appendix K–V. Biosafety Level 3 (BL3)—Large Scale

''Appendix K–V–C. Culture fluids (except as allowed in Appendix K–V–D) shall not be removed from a closed system or other primary containment equipment unless the viable organisms containing recombinant DNA molecules have been inactivated by a validated inactivation procedure. A validated inactivation procedure is one which has been demonstrated to be effective using the organisms that will serve as the host for propagating the recombinant DNA molecules. Culture fluids that contain viable organisms or viral vectors intended as final product may be removed from the primary containment equipment by way of closed systems for sample analysis, further processing or final fill.''

Appendix K–V–F is proposed to read:

''Appendix K–V–F. A closed system or other primary containment equipment that has contained viable organisms containing recombinant DNA molecules shall not be opened for maintenance or other purposes unless it has been sterilized by a validated sterilization procedure except when the culture fluids contain viable organisms or vectors intended as final product as described in Section K–V–C above. A validated sterilization procedure is one which has been demonstrated to be effective using the organisms that will serve as the host for propagating the recombinant DNA molecules.''

I–C. Amendment to Section III–D–6, Experiments Involving More Than 10 Liters of Culture, of the NIH Guidelines

In a letter dated November 6, 1997, Richard A. Knazek, Medical Officer, Clinical Research, National Center for Research Resources, NIH, requested an amendment to Section III–D–6, Experiments Involving More Than 10 Liters of Culture, of the NIH Guidelines. Dr. Knazek proposed an addition of a statement, ''When more than 10 Liters of culture media is to be produced within a GMP-accredited facility for subsequent clinical use, the level of appropriate containment shall be determined by the Institutional Biosafety Committee (IBC) affiliated with the institution where the investigator will perform the clinical manipulation of the vector.'' Dr. Knazek stated the rationale of his request as follows:

''The purpose of this amendment is to prevent an additional layer of bureaucracy from impeding the implementation of an appropriately reviewed and approved gene therapy protocol.

''The risks due to exposure to a gene vector will be greatest at the time when the final media product is either incubated with the target cells (ex vivo transduction) and/or

infused into the recipient (in vivo transduction). The IBC at that clinical institution bears the responsibility of being knowledgeable about attendant risks to the investigator, laboratory and medical personnel, patient and the environment.

''While being produced within a qualified GMP facility, the vector is, by definition, both protected from the environment and prevented from escaping into the environment.

''Clearly, the vector and its proposed use must be scrutinized by an IBC. However, the IBC review of the vector and its protocol is most appropriately performed at the clinical site rather than at the GMP facility. Review by more than one IBC would be redundant.''

Section III–D–6 is proposed to read:

''Section III–D. Experiments That Require Institutional Biosafety Committee Approval Before Initiation

''Section III–D–6. Experiments Involving More than 10 Liters of Culture. The appropriate containment will be decided by the Institutional Biosafety Committee. Where appropriate, Appendix K, Physical Containment for Large Scale Uses of Organisms Containing Recombinant DNA Molecules, shall be used. Appendix K describes containment conditions Good Large Scale Practice through BL3–Large Scale. When more than 10 Liters of culture media is to be produced within a GMP-accredited facility for subsequent clinical use, the level of appropriate containment shall be determined by the IBC affiliated with the institution where the investigator will perform the clinical manipulation of the vector.''

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 DNA recombinant molecule 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 12, 1997.

Lana R. Skirboll,

Associate Director for Science Policy, National Institutes of Health.

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