DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Recombinant DNA Research: Actions Under the Guidelines

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

ACTION: Notice of Actions Under the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines).

SUMMARY: This notice sets forth actions to be taken by the Director, National Institutes of Health (NIH), 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).

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

SUPPLEMENTARY INFORMATION: Today's actions are being promulgated under the NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines). The proposed actions were published for comment in the **Federal Register** on October 16, 1997 (62 FR 53908) and November 19, 1997 (62 FR 61862), and reviewed by the NIH Recombinant DNA Advisory Committee (RAC) at its meeting on December 16, 1997.

I. Amendments to Institutional Biosafety Committee (IBC) Approvals of Experiments Involving Transgenic Rodents Under Section III of the NIH Guidelines

I–A. Background Information and Decisions on Actions Under the NIH Guidelines

Section III–D–4, Experiments Involving Whole Animals, of the NIH Guidelines requires that all transgenic animal experiments obtain IBC approval before initiation. In a correspondence dated April 22, 1997, Dr. George Gutman, an IBC representative of the University of California, Irvine, California, inquired whether experiments involving production or use of transgenic mice under Biosafety Level 1 containment could be initiated simultaneous with IBC notification.

The RAC discussed this issue during its June 1997 meeting, recommending that this requirement be changed to initiation simultaneous with IBC notification. The RAC agreed that the requirement for IBC approval prior to initiation is unnecessary and recommended that the NIH Guidelines should be amended so that: (1) The generation of transgenic rodents under Biosafety Level 1 containment (not all animals) can be initiated simultaneous with IBC notification, and (2) the purchase and use of transgenic rodents should be exempt from the NIH Guidelines. A motion was made that these proposed changes to the NIH Guidelines should be published in the **Federal Register** for consideration at the September 12, 1997, RAC meeting. The proposed action would allow: (1) The generation of transgenic rodents that require Biosafety Level 1 containment to be included under Section III–E, Experiments that Require IBC Notice Simultaneous with Initiation; and (2) the purchase and use of transgenic rodents should be exempt from the NIH Guidelines. The motion passed by a vote of 9 in favor, 0 opposed, and no abstentions.

On September 10, 1997, a letter was received from the American Biological Safety Association requesting that the public comment period for the proposed actions under the NIH Guidelines published in the **Federal Register** on August 20, 1997 (62 FR 44387) be extended for an additional 60 days.

At its September 12, 1997 meeting, the RAC was scheduled to vote on the issues surrounding the amendments to IBC approvals of experiments involving transgenic rodents. Considering the American Biological Safety Association's request to extend the public comment period, the RAC decided to modify the language of the proposed actions and publish the revised version in the **Federal Register** for additional public comment as requested by the American Biological Safety Association. The RAC accepted the proposed actions with the deletion of two words ''and use'' from the language, ''the purchase and use of transgenic rodent * * *'' A motion was made by the RAC to accept the amendments to the NIH Guidelines with regard to: (1) The generation of transgenic rodents under Biosafety Level 1 containment (not all animals) can be initiated simultaneously with IBC notification, and (2) the purchase of transgenic rodents should be exempt from the NIH Guidelines. The motion passed by a vote of 11 in favor, 0 opposed, and no abstentions.

The proposed actions were published in the **Federal Register** on October 16, 1997 (62 FR 53908). On December 2, 1997, a letter was received from C. Geoffrey Davis, Ph.D., Vice President, Research, Abgenix, Inc., Freemont, California, requesting to add two words, ''or transfer,'' to the language of the proposed action published in the **Federal Register** regarding the purchase or transfer of transgenic rodents to be exempt from the NIH Guidelines. In a letter dated December 5, 1997, Richard C. Knudsen, President, American Biological Safety Association, endorsed the proposed action and requested insertion of a statement, ''(See Appendix G–III–M, Footnotes and References of Appendix G),'' to aid individuals in determining the suitability of Biosafety Level 1 containment for their constructs. Appendix C–VI, The Purchase of Transgenic Rodents, is proposed to read:

''The purchase of transgenic rodents for experiments that require BL1 containment (See Appendix G–III–M, Footnotes and References of Appendix G) are exempt from the NIH Guidelines.''

During the December 16, 1997, RAC meeting, the RAC accepted the proposed actions with the amendments requested by Abgenix, Inc. and American Biological Safety Association. The motion passed by a vote of 13 in favor, 0 opposed, and no abstentions.

The actions are detailed in Section I–B—Summary of Actions. I accept the RAC recommendations, and the NIH Guidelines will be amended accordingly.

I–B. Summary of Actions

I–B–1. Amendments to Section III–D–4. Experiments Involving Whole Animals

[Section III–D are experiments that require Institutional Biosafety Committee approval before initiation.]

Section III–D–4–c is added to read:

Section III–D–4–c. Exceptions under Section III–D–4.

Section III–D–4–c–(1). Experiments involving the generation of transgenic rodents that require BL1 containment are described under Section III–E–3, Experiments Involving Transgenic Rodents.

Section III–D–4–c–(2). The purchase or transfer of transgenic rodents is exempt from the NIH Guidelines under Section III–F, Exempt Experiments (see Appendix C–VI, The Purchase or Transfer of Transgenic Rodents).''

I–B–2. Amendments to Section III–E. Experiments that Require Institutional Biosafety Committee Notice Simultaneous with Initiation

Section III–E–3 is added to read:

Section III–E–3. Experiments Involving Transgenic Rodents.

This section covers experiments involving the generation of rodents in which the animal's genome has been altered by stable introduction of recombinant DNA, or DNA derived therefrom, into the germ-line (transgenic rodents). Only experiments that require BL1 containment are covered under this section; experiments that require BL2, BL3, or BL4 containment are covered under Section III–D–4, Experiments Involving Whole Animals.''

I–B–3. Amendments to Appendix C, Exemptions Under Section III–F–6.

A new section, Appendix C–VI, is added to read:

Appendix C–VI. The Purchase or Transfer of Transgenic Rodents.

The purchase or transfer of transgenic rodents for experiments that require BL1 containment (See Appendix G–III–M, Footnotes and References of Appendix G) are exempt from the NIH Guidelines.''

[Appendix C–VI, Footnotes and References of Appendix C, will be renumbered to Appendix C–VII through Appendix C–VII–E.]

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

II–A. Background Information and Decisions on Actions Under 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 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. In 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 Sections 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.''

During the December 16, 1997, RAC meeting, the RAC deliberated and accepted Dr. McGarrity's request. A motion was made to accept the language of the proposed action published in the **Federal Register** on November 19, 1997 (62 FR 61862) for the amendments to Appendix K. The amendments will allow production and harvest of biologically active viral vectors in volumes larger than 10 liters. The motion passed by a vote of 13 in favor, 0 opposed, and no abstentions.

The actions are detailed in Section II–B—Summary of Actions. I accept the RAC recommendations, and the NIH Guidelines will be amended accordingly.

II–B. Summary of Actions

Appendix K–III–C is amended to read:

''Appendix K–III. Biosafety Level 1 (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 amended 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 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–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 amended 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 amended 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 amended 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 amended 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.''

III. Amendment to Appendix M–I, Submission Requirements—Human Gene Transfer Experiments, Regarding Deadline Submission for RAC Review

III–A. Background Information and Decisions on Actions Under the NIH Guidelines

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 regularly scheduled RAC meetings.

To give the RAC sufficient time to review protocols, and to allow the investigators to respond to comments of the primary reviewer, an action is proposed to amend the NIH Guidelines, Appendix M–I, Submission Requirements—Human Gene Transfer Experiments, to include a 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.

During the December 16, 1997, RAC meeting, a motion was made to accept the proposed action regarding deadline submission for RAC review, which was published in the **Federal Register** on November 19, 1997 (62 FR 61862). A note to Appendix M–I, Submission Requirements—Human Gene Transfer Experiments, was amended to read:

''**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.''

The motion passed by a vote of 6 in favor, 0 opposed, and 2 abstentions. To clarify the meaning of this note, NIH/ORDA later modified the amended note to Appendix M–I to read:

''**Note:** NIH/ORDA will accept submission material at any time. However, if a protocol is submitted less than eight weeks before a scheduled RAC meeting and subsequently is recommended for public discussion by the full RAC, the public discussion of that protocol will be deferred until the next scheduled RAC meeting. This eight-week period is needed to ensure adequate time for review by the committee members.''

III–B. Summary of Actions

Appendix M–I. Submission Requirements—Human Gene Transfer Experiments, is amended 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 (Institutional 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:** NIH/ORDA will accept submission material at any time. However, if a protocol is submitted less than eight weeks before a scheduled RAC meeting and subsequently is recommended for public discussion by the full RAC, the public discussion of that protocol will be deferred until the next scheduled RAC meeting. This eight-week period is needed to ensure adequate time for review by the committee members.''

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: February 4, 1998.

Harold Varmus,

Director, National Institutes of Health.

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