DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
NATIONAL INSTITUTES OF HEALTH

MINUTES OF THE RECOMBINANT DNA ADVISORY COMMITTEE (RAC) October 16, 1990

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RECOMBINANT DNA ADVISORY COMMITTEE

MINUTES OF MEETING

October 16, 1990

The Recombinant DNA Advisory Committee (RAC) was convened for its forty-fifth meeting at 9:00 a.m. or October 16, 1990, in Building 31C, Conference Room 6, National Institutes of Health, 9000 Rockville Pike, Bethesda, Maryland 20892. Dr. Gerard J.McGarrity (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public. The following were present for all or part of the meeting:

Committee members:

Candida R. T. Acosta Robert P. Erickson Barbara E. Murray

Ronald M. Atlas E. Peter Geiduschek Robert F. Murray
Al W. Bourquin Martin F. Gellert Leonard E. Post
Michael Brewer Susan S. Hirano Monica Riley
Ira H. Carmen Donald J. Krogstad Moselio Schaechter
Donald C. Carner Brian F. Mannix Nelson A. Wivel
James F. Childress Gerard J. McGarrity (Executive Secretary)
Don B. Clewell R. Scott McIvor

A committee roster is attached (Attachment).

Liaison representative:

Daniel P. Jones, National Endowment for the Humanities

Non-voting agency representatives:

Emily M. Gause, DHHS, Alcohol, Drug Abuse & Mental Health Admin.
Phillip Harriman, National Science Foundation
Elizabeth A. Milewski, Environmental Protection Agency
Henry I. Miller, DHHS, Food and Drug Administration
George P. Shibley, Department of Agriculture
Sue A. Tolin, Department of Agriculture
Ralph E. Yodaiken, Department of Labor

National Institutes of Health staff:

W. French Anderson, NHLBI
Christine Ireland, OD
Kris Kiser, OD
Becky Lawson, OD
Erwin Peters, OD

Others:

Arindam Bose, Pfizer Central Research
Thomas L. Copmann, Pharmaceutical Manufacturers Association
Ron Evans, Environmental Protection Agency
Carol Ezzell, BioWorld
Mark Foglesong, Eli Lilly and Company
Joseph R. Fordham, Nova Nordisk Bioindustrials, Inc.
Jeffrey Fox, ASM News and Biotechnology
Rebecca J. Goldburg, Environmental Defense Fund
Alan R. Goldhammer, Industrial Biotechnology Association
Joseph Van Houten, Pharmaceutical Research Institute
Doug Howell, McDermitt, Will & Emery Law Firm
Dorothy S. Jessop, Department of Agriculture
Attila T. Kadar, Food and Drug Administration
Laura Leach, Animal Health Institute
Rachel E. Levinson, Office of Science and Technology Policy
Mark Lewis, Hill and Knowlton

Tony Lubiniecki, SmithKline-Beecham Pharmaceuticals
William H. McMullen, Nova Nordisk Bioindustrials, Inc.
Margaret Mellon, National Wildlife Federation
John H. Payne, Department of Agriculture
Amy Silliman, Science Magazine
Larry Thompson, Washington Post
Manuel Valenzuela, Meharry Medical College
Erik J. G. Vandelinde, Netherlands Embassy
Lisa White, Blue Sheet
John R. Wood, Department of Agriculture

I. CALL TO ORDER AND OPENING REMARKS:

Dr. Gerard G. McGarrity (Chair) called the meeting of the Recombinant DNA Advisory Committee (RAC) to order at 9:00 a.m., on October 16, 1990. He said a notice of the meeting had been published in the *Federal Register* and that a quorum was present. He noted the meeting would be short in comparison to other RAC meetings and called attention to the agenda. He explained that in recognizing people to speak he would do so in the following order: primary reviewers, secondary reviewers, other members of the RAC, other members of NIH and other Federal Government agencies, and then members of the general public. He noted that the RAC is advisory to the Director of NIH and that times as published on the agenda were tentative.

Dr. McGarrity noted that Drs. Clewell, Erickson, Childress Mulligan and Riley, as well as Mr. Carner, were attending their final meeting as members of the RAC. He noted, however, that due to the process of replacement, they may need to attend future meetings as their term does not officially end until a replacement has been selected by the Secretary of the Department of Health and Human Services. He thanked them for their service on behalf of the Department, the Public Health Service, the National Institutes of Health, and offered personal thanks for the support and counsel they had offered him during his tenure as Chairman.

II. MINUTES OF JULY 31, 1990 MEETING:

Dr. McGarrity then called the committee's attention to tab 1406, and called on Dr. McIvor for his comments on the minutes of the meeting of the RAC which took place on July 31, 1990. Dr. McIvor said he had read the minutes and found them to reflect his recollection of the meeting. However, he noted that it had been suggested at the meeting that certain relevant portions of the minutes of the Human Gene Therapy Subcommittee meeting were to be included as Appendices B, C, and D to the minutes of the full RAC meeting and noted that they were not included at present. He moved the minutes be approved pending the addition of those appendices.

Dr. Wivel noted that the minutes of the Human Gene Therapy Subcommittee meetings are reviewed in a less formal manner than the minutes of the RAC meeting and that this review had not taken place. He assured the committee that as soon as this review was completed by the Chair of the Human Gene Therapy Subcommittee, the material would be appended to the minutes of the July 31, 1990 RAC meeting.

Mr. Brewer said he had a small word change which he would discuss with ORDA staff, but found the minutes to be an accurate reflection of what transpired at the July 31, 1990 meeting.

Dr. McGarrity noted that he had requested that the actual vote tally from a vote which was stated in the

minutes as passing by a "majority vote" be amended to show the exact tally of the vote. Dr.Wivel said this had been done.

Dr. McIvor moved that the minutes be accepted as modified. Dr. Brewer seconded the motion. The motion passed by a vote of 17 in favor, zero against and 1 abstention.

Dr. McGarrity noted that at this point he wished to modify the agenda. He noted that Dr. W. French Anderson was in attendance and was prepared to present a progress report on the human gene therapy trial in progress regarding treatment of adenosine deaminase (ADA) deficiency. He asked Dr. Anderson to make his presentation at this point.

III. PROGRESS REPORT ON HUMAN GENE THERAPY PROTOCOL ON ADA DEFICIENCY:

Dr. Anderson said the first patient to enter the protocol was a 4 year old girl who had her initial treatment with ADA-corrected T lymphocytes on September 14, 1990. He noted there were no side effects noted with this treatment. He said she received her second treatment on October 15, 1990, again with no apparent side effects. He noted that Dr.McGarrity had been afforded the opportunity to visit the patient on the 15th and had also met her father and been able to have a brief discussion with them.

Mr. Carner asked how long this process of apheresis and treatment would continue. Dr. Anderson replied that the protocol calls for monthly infusions at current levels up to six months. At six months, if everything continues going well, the number of injected cells will be escalated and the investigators will begin to look for therapeutic effects. This process is expected to continue for approximately 18 months. Dr. Anderson noted that a second patient has been selected and the decision on when to enter this patient into the trial will be made within two weeks.

Dr. McGarrity thanked Dr. Anderson for the opportunity to meet the patient and for the tour of the facilities that he was given. He noted that seeing an actual patient who is being treated gives one a broader perspective on the deliberations and decisions of the RAC.

IV. PROPOSED REVISION OF APPENDIX K OF THE "NIH GUIDELINES" REGARDING LARGE-SCALE EXPERIMENTS:

Dr. McGarrity called on Dr. Riley to discuss this agenda item. Dr. Riley said the subcommittee on Revision of the *NIH Guidelines* had considered a proposal to revise Appendix K and that this proposal, with certain modifications, would be presented to the RAC. She noted that the proposal could be found beginning on page 37846 of *The Federal Register* dated September 13, 1990. She said the subcommittee recommended acceptance of these revisions to Appendix K with the following changes:

1. The acronym "GILSP," which stands for "Good Industrial Large-Scale Practices," should be changed to "GLSP" to indicate "Good Large-Scale Practices" since this Appendix is not limited to industry specifically, but to all large-scale facilities;

2. Strike the word "industrial" under Appendix K-I, "Selection of Physical Containment Levels," lines 18 and 24 of the first paragraph on page 37847, since the appendix will apply to all large-scale facilities;

3. Under Appendix K-II-A, strike the final sentence, "Processes and equipment should be designed and constructed to assure integrity of the production organism and resulting product," since this does not require explicit expression;

4. Under Appendix K-II-F, add the word "governmental" after the word "applicable" to make the sentence read, "Discharges containing viable recombinant organisms shall be handled in accordance with applicable *governmental* environmental regulations;"

Dr. Riley said that in light of these recommended modifications the subcommittee has asked that ORDA review both the descriptive and tabular material describing the GLSP level to ensure they meet with the levels of containment called for by all four levels in the existing *National Institutes of Health (NIH) Guidelines for Research Involving Recombinant DNA Molecules* as modified. ORDA was also asked to review the footnotes to ensure they meet all modified *NIH Guidelines* and the intent of Appendix K.

Dr. Riley said the subcommittee recommended that the definition of "Good Industrial Large-Scale Practice (GILSP) Organism," as found in Appendix K - Definitions to Accompany Containment Grid and Proposed Modification to Appendix K," be deleted as it is redundant with a definition found earlier in the text.

Dr. Bourquin questioned whether a statement should be added in the form of a footnote that, "This summary table represents *NIH Guidelines* only. Other regulations or guidelines may apply and are not necessarily superseded by the recommendations of this table." He said this would at least make the reader cognizant of the fact that other regulations and guidelines may apply and still be applicable.

Dr. Atlas questioned whether this was necessary since the *NIH Guidelines* are limited to experiments funded by the NIH and that other Federal, state, local, and regulations can be applied independently. He said this type of footnote could be put on the entire *NIH Guidelines*. He suggested perhaps the same intent could be easier dealt with by changing the title of the table to "Summary of Containment Levels Under the *NIH Guidelines*." He noted that in this way, if the table were to be used as a separate table, independent of the rest of the document this would clarify where it came from and to what it refers.

Dr. Clewell said that he agreed in general with the setting up of this category of "Good Large-Scale Practice" and the proposal as modified by the subcommittee.

Dr. McGarrity asked for clarification as to whether the footnotes would remain in the Appendix. Dr. Riley said this was one of the things the subcommittee felt ORDA needed to look at. She said it was anticipated that Footnote 2 would be deleted, but she left that decision up to ORDA. The staff would be responsible for ensuring that the grid and any prose associated with the grid would conform with the existing guidelines for BL1-BL3. In addition, the description in the table for the GLSP level should reflect what is found in the prose passages of Appendix K-II.

Dr. Post said that he was concerned that the text that appears in *The Federal Register* draft is not as complete as the text that appears in the existing Appendix K-II, and stressed the necessity for ORDA to ensure that the prose in the table is transcribed properly from Appendix K-II. He suggested perhaps it would be better for ORDA complete their review before further review by the committee. Dr. Riley said this may provide for a more expeditious review.

Dr. Henry I. Miller of the Food and Drug Administration (FDA) agreed with Dr. Post in his assessment of the notice in *The Federal Register*. He added that FDA had submitted written comments which included minor suggestions, but overall he felt the wording in the notice reflected the contents of the *NIH Guidelines* and was appropriate to the standard levels of practice.

Dr. Riley noted that there were suggestions which were made both in the FDA letter as well as one from Dr. Silverman of the University of California at Los Angeles as to suggested changes in Appendix K-II. She asked Dr. Miller if he would like to comment on the FDA suggestions.

Dr. Miller said the first suggestion the FDA had made was that restricted access should be required for the BL2-LS level. He noted that in most cases it would be unlikely that an organism which requires BL2 containment would not be in a restricted access site at either a university or industrial facility.

Further, Dr. Miller said, that at level BL3-LS HEPA filtration should be required for supplying air to and exhausting air from the work area in Criterion 28. He noted that it would also be unlikely that this would not be already in place at most universities and industrial facilities dealing with organisms requiring BL3 containment.

He added that if the suggestion for HEPA filtration is accepted that some rewording is suggested to get away from a design standard and move towards a performance standard. He suggested the following wording for Criterion 28:

"Supply and exhaust air should be HEPA-filtered, subjected to thermal oxidation, or otherwise treated, to prevent release of viable organisms."

Dr. Mark Foglesong of Eli Lilly & Company agreed with the suggestions presented by Dr. Miller and noted that if these changes are made on the table that it will require going back and making the appropriate changes in the prose in Appendix K of the *NIH Guidelines*.

Dr. Riley said that Dr. Silverman of UCLA suggested adding an explanatory or philosophical statement on page 37847 of *The Federal Register* notice, under Appendix K-I. The sentence would read:

"The four levels set containment conditions at those appropriate for the degree of hazard to health or the environment posed by the organism, as judged by experience with similar organisms unmodified by recombinant DNA techniques and consistent with good industrial large-scale practices."

Dr. Robert Murray seconded Dr. Post's earlier proposal that ORDA make their review and put together all the changes into a final version before the committee is asked to vote on it because of the many changes.

Dr. Riley recommended that the Appendix K modifications be approved with all of the changes recommended and that the modified version come back to the subcommittee for a final review before final adoption. Dr. McGarrity asked for clarification as to whether this meant that the staff would prepare the GLSP level, making it consistent with the rest of Appendix K. Then the subcommittee would review this and, if the subcommittee approves it, it would be brought back at the next meeting of the RAC for final approval. Dr. Riley said this is what she had envisioned.

Dr. McGarrity asked if the suggestions by the FDA and UCLA would be tentatively accepted along with all the other modifications which Dr. Riley presented. She said this would be the case.

Dr. Atlas noted that if the suggestions from FDA to change two requirements in Criteria 14 and 28 were taken this would, in fact, be a change from the current *NIH Guidelines*. He asked if the issues of accepting the suggestion of the FDA and the approval of the table were a single issue to be put before the subcommittee. Dr. Riley said these were separable issues and that they will have to be addressed separately by the subcommittee.

Dr. Miller asked whether it would be possible for the RAC to approve the revision based upon final review and approval by the subcommittee on Revision of the *NIH Guidelines*, rather than to put this issue off until the next full RAC meeting.

Dr. McGarrity asked Dr. Wivel for an interpretation on this proposal by Dr. Miller. He noted that in the past the RAC had required approval of the Human Gene Therapy Subcommittee before allowing a vote of the full RAC on any proposal, but he was not sure whether this ruling was specific only to the Human Gene Therapy Subcommittee. Dr. Wivel said that in practice the RAC does not vote on any matter under discussion by a subcommittee until that subcommittee has cleared it to come before the full committee.

Dr. McGarrity called on Dr. Rebecca Goldburg of the Environmental Defense Fund (EDF) to make comments on the proposed change to the NIH Guidelines. She said the EDF opposed the changes to Appendix K for the following three reasons:

1. The appendix broadens the RAC's focus from small-scale research to large-scale industrial operations;

2. The Environmental Protection Agency (EPA) is currently working on regulations for commercial production of chemicals using biotechnology, and the adoption of this appendix would create a loophole to bypass the EPA rulemaking procedure; and,

3. The proposed GLSPs are inadequate in that some of the provisions are vague and environmentally unwise.

Dr. Goldburg said that she believed the adoption of the proposed amendment to Appendix K would erode RAC's credibility and replicate work already underway at EPA. She noted that steps had been taken this morning to remove the industrial emphasis of this proposed amendment but that it still appears to be an attempt by RAC to provide regulation for industry which is not a role of the RAC.

Dr. Riley pointed out the fact that the *NIH Guidelines* were indeed not regulations and that in fact they explicitly contain language noting that they are not intended to conflict with regulations of other Government agencies. She pointed to Appendix K, and noted that Section K-11-F explicitly states:

"Discharges containing viable recombinant organisms should be handled in accordance with applicable governmental environmental regulations."

Dr. Post noted that although there was never any intention that the *NIH Guidelines* be construed by industry as regulatory, that many companies have voluntarily adhered to them as a matter of company policy. Indeed, they have evolved into a code of practice for the industry.

Dr. Carmen asked how much large-scale research is done at academic institutions. Dr. Riley said she did not have any figures but noted that most large research campuses have large-scale fermentation facilities for the purpose of providing their investigators with materials for their individual use. Dr. McGarrity noted that there were a number of institutions with facilities that would exceed the 10-liter limit. He noted that many would probably be exempt since they are used for cell culture, and he was not sure how many were dealing with recombinant organisms.

Dr. Foglesong pointed out that the *NIH Guidelines* originally designated "large-scale" as being greater than 10 liters, but that nowadays it is not uncommon for universities to have 14-15 liter equipment which they are able to purchase from suppliers off the shelf.

Dr. Elizabeth Milewski of EPA noted that they were in the process of developing regulations to address large-scale fermentation in industry. She suggested that since both EPA and NIH are part of the "Coordinated Framework," she asked that some provision be made for EPA and NIH to work together

under the rubric of the "Coordinated Framework" to discuss this particular proposal to ensure consistency across all the agencies in the way that they are approaching the industrial sector.

Dr. Ralph Yodaiken, Senior Medical Advisor at the Department of Labor (DOL) and the Occupational Safety and Health Administration (OSHA) suggested that DOL and OSHA also be made a part of any interagency committee that is developed to review this proposal. He asked what procedures were in place for reporting accidents and for follow-up of persons who are accidentally exposed.

Dr. McGarrity said that the table associated with Appendix K will not contain any such requirements for the BL1-LS level.

Dr. Joseph Van Houton, of the Robert Wood Johnson Pharmaceutical Research Institute said that the reason medical surveillance is not required at either the GLSP or BL1-LS level is that the organisms being addressed are non-pathogenic. He said that beginning at the BL2 level opportunistic pathogens are involved. Since such organisms pose a risk of infection, medical surveillance is required.

Dr. Yodaiken noted the requirement under OSHA regulations for reporting hospitalizations on an OSHA log. He asked if there were written procedures for follow-up contained in the *NIH Guidelines* or whether each individual facility is left to develop its own procedures.

Dr. McGarrity said no detailed procedure is outlined but that Appendix K-II-J states:

"Institutional codes of practice shall be formulated and implemented to ensure adequate control of health and safety matters."

Dr. McGarrity noted the historical desire of the RAC not to become involved in industrial practice. He briefly summarized the history of the RAC in dealing with industrial experiments in the early 1980s in which proprietary data were looked at in closed executive sessions. He noted that the *NIH Guidelines* had been revised since that time to generally state that all environmental laws should be adhered to and that there should be follow-up on all health and safety matters deferring, when appropriate, to the appropriate Federal regulatory agencies.

Dr. Schaechter said that the EDF had been the only real dissenting voice in the discussion and he wanted to address some of the points they had made in their statement. He noted that the role of RAC and its overlap with other Government bodies has been the subject of concern. In fact, this had been an item of discussion in the regional hearings that the RAC had conducted during the fall. He noted that the RAC had evolved over the years in their outlook towards oversight in relation to that of the regulatory agencies and asked if the EDF had participated in any of the regional hearings.

Dr. Goldburg noted that she had testified on behalf of the EDF in the regional hearing in New York City and had submitted written testimony at that time. Dr. Schaechter said he would re-read that testimony with interest with a view toward these issues.

Dr. Schaechter noted that the subcommittee had disagreed with the second objection of the EDF relative to environmental release in that the *NIH Guidelines* are clear on the issue of the applicability of Government regulation. Dr. Goldburg said that the provisions of the Resource and Recovery Act had never been implemented by EPA to cover infectious waste and that this was a point of specific concern to the EDF. She said, "You can put just about anything down the drain you want." Dr. Schaechter asked for a response from EPA on this point.

Dr. McGarrity reminded the committee that there was a motion on the table made by Dr. Riley. Dr. McGarrity asked that the motion be restated.

Dr. Wivel and Dr. McGarrity discussed the actual motion with the attempt to clarify exactly what revisions to the Appendix were being considered, if any. Dr. Wivel said his view was that Dr. Riley moved acceptance of Appendix K with the modifications suggested, with the proviso that staff assure consistency between the tabular presentation and the prose. The staff will provide a revised document to the subcommittee for Revision of the *NIH Guidelines* prior to consideration by the entire RAC.

Dr. McGarrity put the motion to a vote. The motion passed by a vote of 20 in favor, none opposed and no abstentions.

Dr. Krogstad suggested that Dr. Milewski be in attendance at the next meeting of the subcommittee for Revision of the *NIH Guidelines* to act as a consultant on issues of EPA regulatory oversight. Dr.McGarrity added that if any other members of the committee had concerns or suggestions that they be conveyed to the Chair and he would pass them on to staff.

At this point, Dr. McGarrity called for a brief recess and asked that the RAC reassemble at 10:47 a.m.

Dr. McGarrity reconvened the RAC at 11:00 a.m., and noted that the next item on the agenda would be a discussion of a

preliminary review of the regional hearings conducted by the RAC. He noted that tabs 1402/I, 1403, 1404, 1408, and 1411 contained relevant information.

V. PRELIMINARY REVIEW OF THE REGIONAL HEARINGS CONDUCTED BY THE RECOMBINANT DNA ADVISORY COMMITTEE:

Dr. McGarrity introduced the topic noting that the RAC had conducted seven regional hearings and that Dr. Wivel and he had attended all seven hearings, while other members of the RAC and ORDA staff had been in attendance at meetings which took place at locations convenient for their attendance. He noted that a number of individuals, as well as organizations and commercial firms had submitted both formal written statements as well as oral testimony at these hearings. He noted that this was to be a preliminary report and that a more in-depth report would be presented to the RAC at its February 4, 1991 meeting.

Dr. McGarrity said he felt the meetings had been a truly valuable educational experience, providing a public perception of the RAC and its work. The testimony provided some suggestions of where the RAC should go in the future, which could not have been gotten in any better means than meetings such as these.

Dr. Wivel said that what he wanted to present was a general composite response to the five questions which were published for general comment before the regional meetings. He noted that a broad range of people and organizations were heard from and noted that among some of the most interested persons in all of the meetings were the biological safety officers.

Dr. Wivel then went on to question one:

1. "Should the definition of recombinant DNA be modified to encompass the newer techniques in molecular genetics and should the RAC increase its purview in keeping with this change in definition?"

He noted that about half the people who presented opinions on this question favored modifying the definition and many felt that this would not necessarily increase the purview of the RAC since many of these experiments would still be exempt. However, about half of those persons who testified also felt there was no need to change the definition.

Dr. Wivel continued with question two:

2. "Do the newer techniques in molecular genetics pose any new risks not seen with the established techniques?"

He noted that the resounding response to this question was that there was no indication that any of these techniques posed any new or unique risks.

The third question was:

3. "Should the RAC consider a plan whereby more of the review responsibilities are transferred to the local Institutional Biosafety Committees (IBCs), with fewer review responsibilities for the RAC itself? (An example would involve adding plant pathologists to the IBCs to facilitate consideration of protocols which require environmental release.)"

Dr. Wivel said that in general there was a mixed response to this question. One thing that was clear was that the majority of experiments being submitted to localIBCs are exempt and that the exercise is mainly one of paperwork. He recalled that during the hearings it was noted that the*NIH Guidelines* are incorporated into local laws and regulations. NIH is deemed to be acting as a third party which lends credibility to the local IBCs and facilitates acceptance of their oversight role in the local communities.

The fourth question was:

4. "Under the current system of review, a process-oriented approach is used to identify those experiments which should be evaluated, and a product-based approach is used to determine the level of risks, and thus the level of containment. Is this system adequate or should significant changes be considered to make the process more risk-based?"

Dr. Wivel said the general feeling was that a process-based entry point for oversight applicability and then a product-based risk assessment is seen as a practical way to go, although there was some feeling that a completely product-based assessment would be the ideal.

The fifth question was:

5. "With the advent of gene therapy protocols, is there a perceived need for orientation materials to be provided to the local IBCs?"

Dr. Wivel said that with regard to gene therapy it was obvious that a tremendous gap exists between the research that is ongoing at NIH and the rest of the country with development of human gene therapy protocols. Most people, when questioned, had no anticipation that they would be receiving requests to perform human gene therapy trials. Further, they felt uncomfortable and unqualified to deal with them at this point.

Dr. Wivel said that this last point bears on discussions which have taken place vis-a-vis the role of the

RAC and the Human Gene Therapy Subcommittee relative to their educational functions. Should there be workshops for both IBCs and individual investigators? He noted that one exception was Baylor College of Medicine in Houston where a group is actively planning a human gene therapy protocol. He noted that the group there is well trained and capable of performing such a trial and that the RAC could expect to see a proposal from them within 12-18 months.

Dr. Wivel said that other issues were brought up which deserve comment. One of the most interesting related to the issue of the future of the *NIH Guidelines* and the RAC. He noted that representatives of the FDA, as well as the University of California, had suggested there was sufficient scientific rationale for sunsetting the *NIH Guidelines*, based on over 15 years of experience and knowledge gained in the field of recombinant DNA research.

However, Dr. Wivel noted that these were the only two comments received which expressed this feeling. The overwhelming majority of responses indicated that the *NIH Guidelines* should continue to serve a role as a national code of practice for the field and should be kept in place with timely modifications.

Another important issue outlined by Dr. Wivel was the matter of whether the RAC and theNIH should continue to have a role in reviewing environmental releases. He noted that it is generally perceived that NIH does not have the primary expertise in this area and that other Government agencies have a regulatory role to play in this issue.

Dr. McGarrity thanked Dr. Wivel for an excellent summary of the regional meetings and said he would like to present some overall observations that he had made during the meetings. He said that in general, the RAC received high marks for the job it has been doing. He noted the wide range of constituencies that the RAC has around the country and the world. He said that it was worthy of note that the meetings were not attended by bench scientists, but that the people in attendance were administrators, members ofIBCs, safety officers, and many participants from outside the traditional academic environment, including professional organizations, and members of industry. He also noted that there were a large number of comments from the general public and organizations representing the general public.

Dr. McGarrity noted that the timeliness of modifications to the *NIH Guidelines* and making them easier to understand were of concern, as well as the educational role of the RAC. He stressed that the role of the RAC as a truly public forum was mentioned repeatedly.

Dr. McGarrity said the meetings were educational. He felt they showed that the RAC has well served its mandate, and that it should continue to evolve and serve theNIH and the general public in a productive way in the decade of the 1990s and beyond.

He then called on Mr. Carner to express his views on the meeting in Los Angeles. Mr.Carner said the single most important topic presented at both UCLA and Stanford was the issue ofsunsetting the RAC and the *NIH Guidelines*. He said he believed the RAC should have a study committee assigned to thinking about its future and that such a study should take no more than a year. He said he felt the RAC and the standards that it has set have been too useful to eliminate without careful thought.

Dr. Geiduschek said he came away with the sense that there was no sense of crisis among the participants at the meeting at Stanford and that they felt the RAC served as some protection to them at the local level by being a national group which is available to consider rational scientific issues of biotechnology.

Dr. Carmen noted that the meeting in Chicago included three chairmen ofIBCs who expressed an

opinion that the RAC, over the years, had been unduly process-oriented and that a product-based risk assessment should be given more attention. He said that there was no consideration being given to human gene therapy protocols by the universities represented at the meeting. The feeling was that if such protocols were submitted for IBC review that they would look to theNIH, the RAC and Human Gene Therapy Subcommittee for guidance. He said there was some uncertainty expressed with regard to whether additional review responsibility should be placed on the IBCs at this meeting.

Dr. Hirano said that she noticed a diversity of opinions among the IBCs of the different universities represented at the Chicago meeting in relation to increasing the role of theIBCs in review of recombinant DNA research. She noted that there was confusion voiced by representatives of universities over the issue of planned release experiments. With the advent of USDA Guidelines, there was confusion about where and to whom protocols should be submitted. Further, there is doubt about what is required for approval. She urged that the RAC not withdraw from oversight of planned release experiments until the regulatory agencies can devise a more focused and explicit plan of how to regulate them.

Dr. Krogstad commented on a letter received from Dr. Milton Schlesinger of Washington University. He said the thrust of the letter was "We're doing fine and we can probably do better if you leave us alone." He said this resulted from the huge impact of Monsanto's efforts in genetic engineering which have focused attention on agricultural release and resulted in increased community pressure on Washington University. Further, he said he was not sure that Dr. Schlesinger would be prepared or comfortable to confront a protocol for human gene therapy.

Dr. Krogstad asked if he could comment at this time on the letter from Dr. Robertson Parkman. Dr. McGarrity replied that comments of that nature would be in order. Dr.Krogstad said that he felt it was an intriguing suggestion that the RAC was going through an identity crisis, as well as his suggestion that the RAC and Human Gene Therapy Subcommittee begin to discuss germ line human gene therapy, which does not imply the committee is either in favor or against it, but merely that this is one forum where enough expertise and credibility exists to begin this discussion.

Dr. McIvor said that the Chicago hearing pointed out to him that the*NIH Guidelines* and the RAC were needed to provide expertise in evaluating new techniques and experiments that are arising in the field. He agreed with Dr. Krogstad that Dr. Parkman's comments relative to the RAC being the forum to begin a discussion of germ line human gene therapy was intriguing. He said that he felt this committee was well prepared for dealing with somatic cell human gene therapy because it discussed these issues early on when it was only an abstract concept. To prepare for potential germ line human gene therapy proposals in the future, the committee should begin to consider the issue well before the first protocol arrives.

Dr. McGarrity said that it took 5 years from the time of the development of the*"Points to Consider" for Human Gene Therapy* until a protocol was actually approved. It is difficult to foresee what strides will be made in technology and science in the next 5 years and it is probably time to begin to think about these issues in a systematic manner.

Dr. Post reiterated the points made by Dr. Hirano about the confusion that investigators and local review groups have relative to planned release experiments involving both plants and humans. He stressed that there needs to be some type of very clear guidance so that people know what procedures need to be followed in this regard.

Dr. Riley said she attended the meeting in Boston. She said the major issues were that the RAC should not only continue but expand its purview to the newer technologies, utilizing a more risk-based approach in considering all genetic modification issues, not just recombinant DNA. She noted that the

representatives of local IBCs in the Boston area called for the RAC to continue providing them with advice and counsel in the performance of their duties.

Dr. Atlas said the Boston hearing was interesting to him because it included social scientists and members of the general public. They expressed the view that although the *NIH Guidelines* were not regulatory in the same way that EPA and FDA would have regulatory authority, they were in fact adopted as part of local laws and ordinances. If they were sunsetted they would be locked in place and without a means for modification, these could be a crippling of investigation in the field. He noted that in general there was a call for continuation of the RAC. It was emphasized that the public involvement in the deliberations of RAC was what gave credibility to its actions.

Dr. Atlas noted that IBC chairpersons in attendance had requested that the *NIH Guidelines* be republished to bring together the many amendments and modifications and they requested they be put together in a more readable form. He said the opinion was expressed that if the *NIH Guidelines* and RAC were sunsetted that this would cause unduly restrictive legislation and regulation to fill the void in oversight.

Dr. Bourquin noted that the meeting pointed out the role that the RAC plays in bringing public involvement into all aspects of genetic sciences. There was support for RAC responsibility for the newer techniques in molecular genetics.

Dr. Gellert echoed the points made by Dr. Atlas in regard to the sunsetting of the *NIH Guidelines* and pointed to the fact that if this were to take place, it would leave IBCs without guidance on novel problems that will crop up in research. The result will be divergent standards and investigators will "shop" their protocols among IBCs to avoid those IBCs who are more strict in their standards of review.

Dr. McGarrity called on Dr. Childress to begin discussion of the New York City regional hearing. Dr. Childress said that many issues were summarized already by Dr. Atlas. He said one impression he was left with was the sense that the *NIH Guidelines* play an important role in public assurance and reassurance as well as promoting public participation in science. He said that Dr. Parkman's terminology of an "identity crisis" was perhaps too strong and that what the RAC needs to do is a self-assessment because of changes in science, technology and society. In terms of the comments as to germ line human gene therapy, Dr. Childress pointed out that the *Points to Consider* have already been diluted from their original statements relative to germ line gene therapy. The current statements are vague and amorphous. He said this was of interest to members of the subcommittee. There is concern that now is the appropriate time for these discussions to begin. Public forums and discussions of precisely this issue had been planned in the past but had never come to fruition.

Dr. Atlas noted that a point raised in New York City concerned the interactions of RAC with other Federal agencies as well as the adequacy of local IBCs, particularly in the human gene therapy area. In this type of research, the person submitting the protocol is often the only local expert. For this reason, it was felt tha the Human Gene Therapy Subcommittee plays an important role as a national focus of expertise.

Dr. McGarrity called on Dr. Erickson for a report of his comments on the regional meeting in Houston, Texas. Dr. Erickson noted that he was impressed by the lack of large attendance at these meetings. He felt that it pointed to the fact that the RAC was doing its job and that there was no outpouring of concern b the investigators in the field. He added that the majority of the meeting consisted of a discussion of a potential human gene therapy protocol being developed by an investigator at Baylor College of Medicine and he said it was clear that no one wanted to handle it locally. Dr. Erickson echoed Dr. Atlas' comments in regard to the need to republish the *NIH Guidelines* in a more readable form, preferably indexed for ease

of use.

Dr. Barbara Murray said that she felt the local IBC at Baylor College of Medicine was prepared to deal with the issues surrounding the potential human gene therapy protocol. However, they look to the RAC and the Human Gene Therapy Subcommittee for guidance. She added that the one investigator who did appear at the meeting felt the *NIH Guidelines* still had a role to play and that it should be maintained in some form or fashion. Dr. Clewell said that he agreed with the comments of Drs. Murray and Erickson, noting that this meeting was mainly a free flowing dialogue dealing with the issues of review of human gene therapy protocols.

Dr. McGarrity called on Dr. Acosta to present her feelings on the meeting held on October 15, 1990 at the NIH in Bethesda. Dr. Acosta said she was unable to attend the meeting but that in reading the materials supplied for the meeting she had the feeling that both industry and academia felt comfortable having the *NIH Guidelines* in place and did not want to see the RAC sunsetted. There was a feeling that the RAC needed to continue to evolve. She agreed with Mr. Carner's comments that the RAC should introspectively begin looking toward its role in the future and that the RAC Guidelines should be made into a more readable form.

Mr. Brewer said the meeting in Bethesda merely reflected what was heard in other regional meetings with perhaps a bit more emphasis on the international implications of the *NIH Guidelines*, particularly as they relate to the European Economic Community and U.S.-Japan relationships.

Mr. Mannix said he was unable to attend the meeting in Bethesda, however he suggested the RAC reconsider its role with the IBCs and shift its role from being a "parent" of the IBCs, to becoming a "council" of the IBCs, and that the IBCs themselves through this "council" be given more responsibility for effecting an evolution of the *NIH Guidelines* for the future.

Dr. Robert Murray said that he was impressed by the clear message presented in testimony yesterday tha the RAC should remove itself from review of environmental release experiments as well as the feeling that risk assessment become more product-oriented in the future. He noted that the consensus of the group which met yesterday was that the RAC should continue to exist and that the *NIH Guidelines* be kept in place. He reiterated the comments made by Mr. Brewer on the international aspects which were discussed. He said that one thing which was noted by nearly all the participants was the flexibility and adaptability that the RAC has possessed over its history and the feeling was that this was an important trait that any future organization, which may replace the RAC, should maintain.

Dr. Robert Murray also noted that with respect to Dr. Parkman's letter calling for the need to begin to address germ line human gene therapy, that the RAC had already made a statement on this issue. "The RAC and the Human Gene Therapy Subcommittee will not, at present, entertain proposals for germ line alterations." Inclusion in the *"Points to Consider"* Document) He noted that this statement was made because of the strong negative reaction of groups who see eugenic implications in this type of research. He underlined that there was a strong negative feeling at present about germ line human gene therapy. He felt there was concern that to begin such a debate would lend credence to the fears of these groups that such experimentation would ultimately be undertaken.

Dr. McGarrity said he felt this was a good recapitulation of the discussions which took place in the regional hearings and that a detailed report would be prepared for presentation at the next meeting of the RAC. He noted that any one of these areas could be debated at length and asked if the committee wished to have a short discussion on any topics that had been brought up.

Dr. Robert Murray said that one area that was clearly brought up several times was the necessity for RAC to begin to evaluate itself and develop a strategy for its future role. He suggested that rather than waiting for the February meeting that, if not out of order, he would move that a subcommittee be established to begin this process.

Dr. McGarrity cautioned that subcommittees of the RAC are established through its Charter and that the committee cannot itself establish additional subcommittees.

Dr. Robert Murray then moved an *ad hoc* subcommittee be established for this purpose. Mr.Carner seconded the motion saying that it was both timely and important.

Dr. Wivel suggested that the term "working group" would be a better way to couch the identity of such a group to fit within the framework of the Charter for the RAC, and questioned the ability of any committee to critically evaluate itself. Dr. Robert Murray pointed to the fact that most legitimate professional groups do have self-study groups and that if necessary outside critique of any self-study could be obtained.

Dr. Barbara Murray cautioned that by setting up such a group decisions on many concrete issues may be put on hold until the self-study is completed and she felt there should be a mechanism in place to assure timely decisionmaking on these issues.

Dr. Childress suggested that a group be established to review the discussions and testimony obtained in the regional hearings and present recommendations back to the RAC, but that it was apparent some group needed to be set up to begin to sort out the key issues and arguments so that the committee as a whole can then evaluate them.

Dr. Geiduschek noted that it was clear that the RAC operates under a Charter from the Department of Health and Human Services (DHHS). There are always certain questions which are to be evaluated. Regardless of the answers obtained to said questions the RAC will be unable to act, due to the fact that it functions in an advisory role and has no authority for action. Therefore the outcome of any self-study can only be to provide information to others who do have the authority to act, i.e., the Director of NIH and the Secretary of DHHS.

Dr. Robert Murray said that the basis for his motion was to take into consideration the opinions expressed in these regional hearings and formalize them so that RAC can decide on whether it should continue with business as usual or whether some changes should be made and that such recommendations would indeed be forwarded to the Director of NIH and the Secretary of DHHS.

Dr. McGarrity asked if the group would be expected to deal with specific points in regard to revision of the *NIH Guidelines* which are in progress and were part of the discussion at the regional meetings such as the proposed new definition of "recombinant DNA" and oversight of environmental release which have been under study by chartered subcommittees.

Dr. Robert Murray said he felt the thrust of the group that he was proposing would be to discuss the composition and function of the RAC as opposed to specific changes to the *NIH Guidelines*. He added that some of these issues could impact on those assessments but that they would not be themselves the focus of the group.

Dr. Carmen asked if Dr. R. Murray considered that there would be a dual inquiry, one dealing with the questions discussed at the regional meetings and another dealing with the overall issue of the composition and overall function of the RAC. Dr. Robert Murray said that these issues do intertwine but he

felt they could be dealt with by such a working group. Dr. Carmen said he disagreed with a dual approach noting that the RAC had many problems before it of great importance, such as the relationship between the RAC and the Human Gene Therapy Subcommittee which must be considered within the next six months.

Dr. Riley asked for clarification on the issue of changing the definition of "recombinant DNA." Dr. McGarrity said that this was one of the questions posed at the regional hearings and that he expected the summary of the regional hearings would include a summary of feelings on this issue which can then be acted on by the RAC as it sees fit during its deliberations. Dr. Robert Murray said he did not feel this issue was impacted by his motion and that really his motion was in response to more general issues raised in the regional hearings and to show the public that the RAC does react to suggestions from the public.

Dr. Murray underlined that the proposed working group would not make any report based on the summary presented at the February meeting of the RAC, but is being established to begin a process of introspective self-examination to begin to look at the future role of RAC.

There was a short discussion of the issue of whether the RAC would be voting on the recommendations of the subcommittee on Revision of the *NIH Guidelines*. Dr. McGarrity said that this would be on the agenda for the February meeting of the RAC.

Dr. McGarrity put Dr. Robert Murray's motion to establish a working group to study the future role of the RAC to a vote. The motion passed by a vote of 14 in favor, 6 opposed, and no abstentions.

Dr. McGarrity asked if anyone had any other business. Dr. Schaechter said he was concerned with the relationship of the subcommittees to the parent committee. He pointed out that in the past a great deal of discussion had taken place in the Human Gene Therapy Subcommittee with regard to the protocols for human gene therapy and when the proposals came before the RAC discussion seemed to be limited and brief. He said he was worried that if the subcommittees were empowered to do most of the work that they would take on a life of their own and eventually bypass the role of the parent committee.

Dr. Wivel noted that in the instance being discussed that these two meetings took place in a back-to-back fashion. Many of the members of the parent committee were in attendance for the meeting of the subcommittee. He assured Dr. Schaechter that this would not be the case in the future and that this was done to accommodate the investigators in an ongoing protocol and is not seen as a practice that will continue in the future.

Dr. Wivel noted that three protocols are on the agenda for the next meeting of the Human Gene Therapy Subcommittee and that the subcommittee has a working group which is wrestling with determining deadlines for timely submission of protocols so that they can be considered in a more orderly fashion.

Dr. Barbara Murray asked for assurance that the issue of the proposed new definition of "recombinant DNA" would be on the table for the next meeting of the RAC. Dr. McGarrity noted that anyone, including the members of the subcommittee, could request that something be placed on the agenda for the RAC. Dr. Wivel assured Dr. Barbara Murray that this agenda item will be noted in *The Federal Register* as an agenda item for the February 4, 1991 meeting of the RAC.

VI. FUTURE MEETING DATES OF THE RECOMBINANT DNA ADVISORY COMMITTEE:

Dr. McGarrity called the committee's attention to the future dates of the RAC which could be found in tab 1405. He noted that the next meeting would be held on February 4, 1991. He also reminded the

committee that the Human Gene Therapy Subcommittee would be meeting next on November 30, 1990.

VII. ADJOURNMENT:

Dr. McGarrity thanked the committee members for their participation in the regional hearings and called particular attention to the efforts of Dr.Wivel and Becky Lawson in making these regional meetings a success. He also thanked all of the host institutions for providing facilities for the regional meetings.

Having concluded the agenda and there being no further business to be discussed, Dr. McGarrity adjourned the Committee at 12:36 p.m., on October 16, 1990.

Nelson A. Wivel, M.D.
Executive Secretary

I hereby acknowledge that, to the best of my knowledge, the foregoing Minutes and Attachments are accurate and complete.

Date: 2/4/91

Gerard J. McGarrity, Ph.D.
Chair
Recombinant DNA Advisory Committee
National Institutes of Health