DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
RECOMBINANT DNA ADVISORY COMMITTEE
MINUTES OF MEETING
December 9, 1996

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The Recombinant DNA Advisory Committee (RAC) was convened for its sixty-fifth meeting at 9:00 a.m. on December 9, 1996, at the National Institutes of Health (NIH), Building 31, Conference Room 10, 9000 Rockville Pike, Bethesda, Maryland 20892. Dr. LeRoy B. Walters (Chair) presided. In accordance with Public Law 92-463, the meeting was open to the public on December 9 from 9 a.m. until 4:30 p.m. The following were present for all or part of the meeting:

Committee Members:

Gary A. Chase, Georgetown University Medical Center
Patricia A. DeLeon, University of Delaware
Joseph Glorioso, University of Pittsburgh
Rochelle Hirschhorn, New York University School of Medicine
Michael M. C. Lai, University of Southern California
M. Therese Lysaught, University of Dayton
Kathleen M. McGraw, State University of New York at Stony Brook
Abbey S. Meyers, National Organization for Rare Disorders
Arno G. Motulsky, University of Washington
Robertson Parkman, Childrens Hospital of Los Angeles
Gail S. Ross, Cornell University Medical Center
Karen Rothenberg, University of Maryland School of Law
Bratin K. Saha, Emory University
R. Jude Samulski, University of North Carolina, Chapel Hill
Brian R. Smith, Yale University
Stephen E. Straus, National Institutes of Health

LeRoy B. Walters, Kennedy Institute of Ethics, Georgetown Univ.
Doris T. Zallen, Virginia Polytechnic Institute and State Univ.

Executive Secretary:

Debra W. Knorr, National Institutes of Health
A committee roster is attached (Attachment I).

Non-Voting Representative:

Philip Noguchi, Food and Drug Administration

National Institutes of Health Staff:

Deborah Applebaum-Bowden, NHLBI
Tina Blakeslee, OD
Connie Bowers, OD
Christine Grady, CC
Margie Grubb, OD
Troy Hayes
Christine Ireland, OD
Debbie Jackson, OD
Melody Lin, OD
Catherine McKeon, NIDDK
Anne Phelps, OD
Fran Pollner, OD
Thomas Shih, OD
Sonia Skarlatos, NHLBI
Lana Skirboll, OD
Bernard Talbot, NCRR
Harold Varmus, OD

Others:

Robert Anderson, Food and Drug Administration
Dale Ando, Chiron Corporation
Elizabeth Austin, Glaxo Wellcome, Inc.
Beth Baker, Bioscience Magazine
Kameron Balzer, Genentech, Inc.
Bridget Binko, Cell Genesys
Amy Bosch, Targeted Genetics Corporation
Robert Boyd, Knight-Ridder, Inc.
Andrew Braun, Massachusetts General Hospital
Jeff Carey, Genetic Therapy, Inc.
Kenneth Culver, Codon Pharmaceuticals, Inc.
John Cutt, Schering-Plough Research Institute
Mary Davidson, Alliance of Genetic Support Groups
Dean Engelhardt, Enzo Biochem, Inc.
Diane Fleming, Biosafety Consultant
Jeffrey Fox, Science Writer

Gerald Gottlick, U.S. Medicine
Tina Grasso, GenVec
Philip Harriman, National Science Foundation
James Hawkins, Hawkins and Associates
Edie Irvine, Genetic Therapy, Inc.
Susan Jenks, Journal of the National Cancer Institute
Deborah Kochevar, United States Senate, Congressional Fellow
Hitoshi Kotani, Genetic Therapy, Inc.
Steven Kradjian, Vical, Inc.
Alexander Kuta, Genzyme Corporation
Michael Langan, National Organization for Rare Disorders
Rachel Levinson, Office of Science and Technology Policy
Edie Irvine, Genetic Therapy, Inc.
Tony Marcel, TMC Development
Gerard McGarrity, Genetic Therapy, Inc.
Bradie Metheny, Washington Fax
Andrea Neuman, Technology Catalysts International Corporation
Jeffrey Ostrove, Microbiological Associates
Amy Patterson, Food and Drug Administration
Theresa Pierson, Biotechnology Consultant
Stephen Pijar, University of Maryland
Reginald Rhein, Scrip World Pharmaceutical News
Joseph Rokovich, Somatix Therapy Corporation
Lisa Seachrist, American Health Consultants
Tomiko Shimada, Ambience Awareness International, Inc.
Allan Shipp, Association of American Medical Colleges
Helen Shu, Systemix
Dominick Vacante, Magenta Corporation
Meredith Wadman, Nature Magazine
Joan Weiss, Alliance of Genetic Support Groups
Lisa White, The Blue Sheet
Carolyn Wilson, Food and Drug Administration
Celeste Zalewski, Technology Catalysts International Corporation

I. CALL TO ORDER AND OPENING REMARKS

Dr. LeRoy Walters (Chair) called the meeting to order. He stated that the notice of the meeting was published in the *Federal Register* on November 4, 1996 (61 FR 56701); and the *Proposed Actions* under the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* were published in the *Federal Register* on November 22, 1996 (61 FR 59725). He noted that a quorum was present and outlined the order in which speakers would be recognized: (1) RAC members, (2) liaison members from other Federal agencies, (3) the public who have submitted written statements prior to the meeting, and (4) the public at large.

Dr. Walters explained that the RAC was responsible for considering the *Proposed Actions* published in the *Federal Register* and submitting its recommendations on the proposal back to the NIH Director. Following discussion of the *Proposed Actions*, the RAC would discuss relevant human gene transfer experiment information that has been submitted to the NIH Office of Recombinant DNA Activities (ORDA) since its last meeting on December 4-5, 1995. He thanked the staff of the ORDA for continuing the ORDA functions since its former director, Dr. Nelson A. Wivel, retired from the Federal government and has

accepted a position at the University of Pennsylvania on June 30, 1996. He thanked Dr. Lana Skirboll, Associate Director for Science Policy, NIH, and Dr. Harold Varmus, NIH Director, for their careful reading of each written comment that was submitted in response to the *Notice of Intent To Propose Amendments to the NIH Guidelines Regarding Enhanced Mechanisms for NIH Oversight of Recombinant DNA Activities* published in *Federal Register* on July 8, 1996 (61 FR 35774).

Dr. Walters noted four items of interest that were included in the meeting material: (1) The *Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy*, December 7, 1995, (co-chaired by Stuart H. Orkin, M.D. and Arno G. Motulsky, M.D.); and (2) A compilation of the human gene transfer experiments submitted to ORDA since its December 4-5, 1995, meeting. A total of 27 new gene transfer protocols were submitted including 1 gene marking protocol, and 26 gene therapy protocols (22 for cancer, 3 for human immunodeficiency virus (HIV), and 1 for X-linked severe combined immunodeficiency (SCID)). Dr. Walters noted that a total of 167 gene transfer protocols have been registered with ORDA to date including 28 gene marking protocols, and 139 gene therapy protocols (17 for HIV, 25 for monogenic diseases, 94 for cancer, and 3 for other diseases/disorders). (3) The publication entitled: *Gene Therapy in the United States: A Five-Year Status Report*, Human Gene Therapy, Vol. 7, pp. 1781-1790, 1996. (4) An announcement of the next two scheduled meetings of the National Bioethics Advisory Commission (NBAC) subcommittees: the Human Genetics Subcommittee meeting on December 13, 1996, and the Human Subjects Subcommittee meeting on December 16, 1996. Dr. Walters noted that two former RAC members, Dr. James F. Childress and Mr. Alexander M. Capron, are currently serving as members of the NBAC. Dr. Childress will be chairing its Human Subjects Subcommittee.

II. MINUTES OF THE DECEMBER 4-5, 1995, RAC MEETING

The RAC approved a motion made by Dr. Ross and seconded by Dr. DeLeon to accept the December 4-5, 1995, RAC minutes (with the incorporation of minor editorial changes) by a vote of 16 in favor, 0 opposed, and 1 abstention.

III. OVERVIEW OF *PROPOSED ACTIONS*

Dr. Varmus presented an overview of the *Proposed Actions*. He noted that he had conducted an extensive analysis over the past 18 months of NIH oversight and funding of gene therapy research. This analysis included the establishment of two committees: (1) the Panel to Assess NIH Investment in Gene Therapy Research (co-chaired by Drs. Stuart Orkin and Arno Motulsky), and (2) the RAC *Ad Hoc* Review Committee (chaired by Dr. Inder Verma). These committees were established based on concerns that the promise of gene therapy was being oversold to the public, and that the "NIH stamp of approval" would be perceived as an acknowledgment that such protocols represented scientific excellence. The NIH "approval" of such experiments contradicts Federal streamlining initiatives, as it duplicates the efforts of the Food and Drug Administration (FDA), which retains statutory authority for such approval.

Dr. Varmus explained that a preliminary proposal, the *Notice of Intent to Propose Amendments to the NIH Guidelines Regarding Enhanced Mechanisms for NIH Oversight of Recombinant DNA Activities*, was published in the *Federal Register* on July 8, 1996 (61 FR 35774). A total of 71 written comments were submitted in response to the *Notice of Intent*. These comments reflected a broad range of public opinions on the proposed changes. Comments were received from a variety of stakeholders, including individuals representing academia, industry, patient advocacy organizations, professional scientific societies, ethicists, other Federal agencies, NIH-funded investigators, past and present RAC members, and private citizens. After careful consideration of these comments, NIH published the *Proposed Actions under the NIH Guidelines* (61 FR 56701). The *Proposed Actions* reflects both public opinion and an intent to increase the effectiveness and efficiency of public discussion of gene therapy research. Specifically,

because of the historical importance of the RAC as a public platform for discussion of human gene therapy research, the *Proposed Actions* encompassed the following elements: (1) retain the RAC, while modifying its roles and responsibilities relevant to human gene therapy research; (2) continue RAC discussion of novel human gene transfer experiments without RAC approval of individual human gene transfer experiments; (3) reduce the membership of RAC from 25 members to 15 members; (4) regularly convene the Gene Therapy Policy Conferences (GTPCs); and (5) maintain public access to human gene transfer clinical trial information.

IV. RAC DISCUSSION OF *PROPOSED ACTIONS*

Dr. Parkman inquired about potential feedback mechanisms for obtaining relevant information about human gene transfer experiments after they have received Investigational New Drug (IND) approval from the FDA. Specifically, for any protocol reviewed by the full RAC, there must be a mechanism by which the investigator notifies the NIH regarding the extent to which RAC recommendations were incorporated into the final protocol. In the event that the RAC's recommendations were not taken into consideration by the FDA, the investigator should provide a detailed explanation regarding such a decision to the NIH. For human gene transfer experiments that have not undergone RAC review, investigators should be required to notify the NIH of any modifications that were incorporated prior to receiving final FDA approval. He noted that it is likely that such experiments will undergo many modifications prior to receiving FDA approval. Dr. Varmus asked Dr. Noguchi to respond to Dr. Parkman's concern. Dr. Noguchi responded that the FDA will provide a summary to the RAC regarding the actions taken by FDA in response to RAC recommendations of any protocol receiving full RAC review. Ms. Knorr noted that current reporting requirements could be modified to require that investigators provide the relevant information to the RAC.

Ms. Rothenberg inquired how the RAC might discuss a novel protocol, e.g., one involving *in utero* gene therapy. Dr. Varmus emphasized that the RAC plays a critical role in anticipating novel approaches and future applications, e.g., proposals to use lentivirus-based vectors, the development of new animal models of disease, and *in utero* applications. He encouraged the RAC to begin its discussions of novel applications well in advance of such submissions. The GTPC will provide an excellent forum for debating novel applications of gene therapy research. In turn, the RAC should develop guidance for subsequent incorporation into Appendix M, *The Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules into One or More Human Subjects (Points to Consider)* of *the NIH Guidelines*. Dr. Noguchi agreed that the GTPCs will serve a very important function to formulate gene therapy policy in anticipation of protocol submission; such open GTPC discussion will help FDA in dealing with a particular protocol when it is submitted to FDA. Ms. Rothenberg asked whether the FDA had the authority to hold a novel protocol, e.g., *in utero* gene therapy, until GTPC recommendations could be developed into policy. Dr. Noguchi responded that FDA would hold the protocol until there was ample public discussion.

Ms. Rothenberg inquired as to Dr. Varmus' reasoning for establishing the GTPCs as an entity separate from the RAC. Continuity would be ensured if GTPCs were considered as an integral component of the RAC's activities. Dr. Varmus responded that the RAC has to deal with other issues such as identification and discussion of novel protocols and enhancement of data management activities. GTPCs should be considered a forum for policy development well in advance of actual protocol submission. GTPCs could be held in conjunction with RAC meetings. Dr. Varmus stated that GTPCs would include numerous *ad hoc* experts to discuss a specific GTPC topic. Ms. Rothenberg asked if GTPCs and the RAC could be integrated such that RAC would set the agenda for the GTPC. Dr. Varmus said that he envisioned GTPCs functioning as workshops involving experts of a particular subject. Dr. Parkman agreed with Ms. Rothenberg's suggestion that GTPCs and the RAC should be closely linked.

Dr. Ross raised the issue of RAC approval of individual protocols, specifically that NIH approval authority will be relinquished under the *Proposed Actions*. Dr. Varmus stated that NIH is not a regulatory agency, and it is more useful for the RAC to provide an oversight role relevant to gene therapy research, closely monitoring the field and developing policy for the safe and proper conduct of gene therapy research.

Dr. Lysaught stated that it would be optimistic to expect that policy development on complex issues, such as germ-line gene therapy, could occur during the course of a single GTPC. Policy formation of such issues should be shaped by deliberation in an incremental fashion over time. She said that the RAC should define its future roles and responsibilities for this area of research. Dr. Varmus said that he did not expect difficult issues such as germ-line gene therapy to be resolved in a single GTPC meeting; simpler topics, such as the use of lentivirus vectors, could be effectively dealt with in a one day conference. At the conclusion of the conference, recommendations could be developed for the NIH Director regarding a specific subject.

Dr. Glorioso inquired about who would be responsible for ensuring the scientific merit of gene therapy protocols. Many protocols are undertaken at academic institutions, but are sponsored by companies that are not producing high quality scientific information. These scientifically inadequate protocols are being approved by the local Institutional Review Boards (IRBs). There should be a single review that would be responsible for assessing the scientific merit of these protocols. Safety should not be the only consideration when approving gene therapy proposals. Dr. Varmus responded that NIH is not directly involved in funding decisions relevant to protocols that are sponsored by the private sector; however, the RAC will play an important role in summarizing clinical trial results when such studies are conducted in collaboration with NIH-funded institutions.

Dr. Zallen expressed concern about shaping gene therapy policy through the GTPCs absent deliberation of a specific protocol. She cited her experience relevant to drafting the *Points to Consider* of the *NIH Guidelines* in 1989 for the first human gene transfer experiment. She suggested that GTPCs should be closely integrated with the RAC.

Ms. Meyers asked if the proposed reduction in the number of RAC members is justified since diverse expertise will still be required. Dr. Varmus responded that the proposed reduction in RAC members is intended to increase the efficiency of RAC discussion and is in line with the committee's reduced responsibilities for individual protocol review and approval. Although the number of RAC members will be reduced, there will be no change in the proportion of committee representation, i.e., public versus scientific members. Ms. Meyers stated that at the conclusion of RAC discussion of a protocol there should be a vote to register the consensus of the RAC, and RAC recommendations should be transmitted to the Office for Protection from Research Risks (OPRR), in addition to the NIH Director. Dr. Varmus noted that the RAC has accumulated a certain moral authority, and its recommendations will be taken into consideration by Federal agencies including OPRR. Ms. Meyers noted her concern that several novel protocols, including the use of poxvirus vectors, were solely reviewed by FDA without RAC public review. Ms. Knorr pointed out that such inconsistencies will be avoided in the future if these *Proposed Actions* are promulgated by the NIH Director. Under the proposed oversight mechanism, the decision regarding whether a protocol is novel will be determined by the RAC.

Dr. Straus stated that the public has a vested interest in human gene therapy, and the RAC is a public forum for its deliberation. He was concerned about the follow-up of RAC recommendations after a protocol receives final FDA approval. Investigators and sponsoring institutions should be required to report all amendments to the protocol after FDA interaction and any adverse events to the RAC. RAC reporting of such information is critical to maintaining public accountability since FDA reviews are conducted in a proprietary manner, i.e., shielded from public review. Dr. Varmus agreed that public

accountability is paramount.

Dr. Hirschhorn noted that gene therapy research differs from other pharmaceutical developments in several aspects including public perception, novelty, and development within academic institutions with NIH funding. Dr. Hirschhorn remarked that participation of experts in the GTPC is useful; she was uncertain what role the RAC would play in the GTPC forum. She was concerned that there are many different national committees dealing with biomedical ethics without a framework of coordination.

Dr. Smith stated that he supported the *Proposed Actions*. Any novel protocol will be highlighted and discussed by the RAC in public. He favored a series of votes on a specific protocol at the end of RAC discussion addressing different aspects of the protocol such as safety, scientific merit, and the Informed Consent document. In case of a split vote, he favored a statement of the minority opinion.

Dr. Smith noted a letter dated November 20, 1996, from Dr Andra Miller of FDA, stating that FDA does not accept Appendix M in place of an IND application, and that the FDA should not be included in the decision making process to identify protocols for full RAC review. Dr. Smith said that the *Proposed Actions* would allow an opportunity for the FDA to request that an individual protocol undergo RAC review. Dr. Noguchi noted that Appendix M of the *NIH Guidelines* is not an official FDA document. Dr. Smith noted that the annual data reporting process would most likely identify potential problems and scientific opportunities in the area of human gene therapy. He asked if the RAC could play a role in assisting the NIH Director in identifying promising research initiatives worthy of funding. Dr. Varmus agreed with Dr. Smith and encouraged the RAC to suggest GTPC topics, e.g., development of more appropriate animal models and alternative or improved approaches to gene therapy research.

Dr. Chase expressed his support for the *Proposed Actions*. He stated that the RAC plays a necessary role with regard to public oversight of gene therapy research in the face of a strong industry profit motives. He emphasized the importance that the RAC should be an integral part of the GTPCs.

Dr. Lai supported the *Proposed Actions,* but noted that there is the need for a mechanism to evaluate the scientific value of ongoing and completed gene therapy protocols and to evaluate efficacy.

Dr. Parkman stated that the GTPC can formulate general guidance for the use of novel vectors such as lentiviruses. He noted the importance of developing RAC stipulations for approval and subsequent follow-up of these stipulations by investigators. This information has been critical for RAC review of similar protocols and will likely continue to be important in the future. This "feedback mechanism" will be absent if FDA resolves relevant issues in a proprietary fashion.

Ms. Rothenberg stated that she is sympathetic to the NIH Director's decision about eliminating "approval" of individual protocols; however, a mechanism has not been clearly developed that will ensure that GTPC recommendations and RAC guidance will be integrated into the FDA regulatory process. The NIH process should have some "teeth" so that public interest can be protected. Bad science is unethical. Dr. Varmus responded that the best way to work out the details of the process is to convene the first GTPC as a trial run to discuss forthcoming issues such as *in utero* gene therapy and lentiviruses.

Ms. Rothenberg said that the current process by which protocols are determined exempt from RAC review is arbitrary. In the *Proposed Actions,* she was concerned about the "majority" vote needed for a recommendation for full review. Each RAC member will have a different viewpoint regarding the novelty of a particular protocol. Ms. Meyers stated her concern about the majority rule since the public members represent a minority of the RAC, and their views may be different from those of the scientific members. Dr Varmus agreed that the minority opinion would be important; a rational explanation regarding novelty of a

protocol would be useful.

Dr. Motulsky stated that public response to the July 8, 1996, *Notice of Intent*, suggests that the RAC could serve as a model for other areas of clinical research in addressing societal concerns. Somatic gene therapy research has evolved into the mainstream of medical research; many of the early concerns pertaining to gene therapy have been resolved. The GTPCs are an excellent idea, and it should not be too closely integrated into the RAC process.

Dr. Varmus stated that he sensed from RAC comments a strong support for the fundamental concepts of the *Proposed Actions*, but there are significant procedural concerns that need to be resolved during the remainder of the meeting. He thanked the RAC members for their thoughtful comments and continued discussion.

Dr. Walters thanked Dr. Varmus for addressing the RAC.

V. OVERVIEW OF *NIH GUIDELINES* MODIFICATIONS

Dr. Skirboll stated that the *Proposed Actions* outlined the future functions of the RAC. She stated that she anticipates that the RAC will fill in the details relevant to its future operation during the course of its discussion. She clarified that the recommendations of the GTPC will be reported to the NIH Director; however, the RAC will play a key role in developing GTPC recommendations into relevant policy for incorporation into the *NIH Guidelines*. An additional target audience of RAC discussion may be NBAC. Many issues raised by the RAC are broader than just gene therapy, and NBAC might consider expanding on these issues. The Human Subjects Subcommittee is likely to be responsive to RAC recommendations; she noted that its Human Subjects Subcommittee is chaired by Dr. Childress, a former RAC member.

Overview of the *NIH Guidelines* Modifications

Ms. Knorr presented an overview of the *NIH Guidelines* modifications. She noted that the specific changes are indicated in the redline/strikeout version included in the meeting material.

Section I-A-1-a. This section describes the process by which human gene transfer experiments will be registered with NIH/ORDA. Upon receipt of a protocol submission, NIH/ORDA will immediately prepare a comprehensive summary sheet that provides specific comparisons to previously submitted protocols. The summary sheets will be faxed to all RAC members for subsequent recommendations regarding the necessity of full RAC review. Upon request, individual RAC members will receive any additional material deemed necessary for review. If full RAC review is recommended by a majority of the RAC, the recommendation will be transmitted to the NIH Director. The NIH Director will make a final decision regarding RAC review of individual protocols.

Section I-D. *Compliance with the NIH Guidelines*. This redlined section has not been changed. This language had been moved to a more appropriate section of the *NIH Guidelines* for the purpose of clarification.

Section III. *Experiments Covered by the NIH Guidelines*. This section describes the types of experiments that are covered by the *NIH Guidelines*. A new section, Section III-C, has been established for experiments that require Institutional Biosafety Committee (IBC) approval, IRB approval, and NIH/ORDA registration before initiation. Section III-A-2, *Human Gene Transfer Experiments*, has been deleted to accommodate the revised procedure for NIH protocol submission and review. Section III-C

defines the proposed protocol registration process, i.e., the submission requirements and the process determining whether a protocol requires full RAC discussion. A sentence was inserted to state that the RAC prefers that information provided in response to the *NIH Guidelines* should not contain proprietary data or trade secrets, enabling all aspects of the review to be open to the public. Dr. Straus was concerned that this statement might preclude the RAC from seeing proprietary information although the RAC is entitled to access such information as a special government employee.

Ms. Knorr noted that full RAC review of an individual protocol may be recommended by: (1) a majority of the RAC, (2) other Federal agencies, (3) the Principal Investigator, or (4) the sponsoring institution. Dr. Parkman noted his objection to allow the principal investigator or the sponsoring institution to recommend full RAC review. Dr. Parkman expressed concern about the NIH Director's role relevant to determining the necessity for full RAC review.

Section III-C has been modified to clarify the requirements for IBC approval of individual gene transfer protocols. IBC approval must be obtained from any institution responsible for constructing or handling the recombinant DNA material to be used in such experiments. As previously suggested in written comments submitted by Dr. A. Dusty Miller, IBC approval shall be obtained from: (1) any institution involved in the production of vectors for human application, (2) any institution at which there is *ex vivo* transduction of the recombinant DNA material into target cells for human application, and (3) any institution at which the recombinant DNA material will be directly administered to human subjects. Dr. Zallen stated that the term "any" should be replaced by the term "every" for clarification.

Section III-C-1. *Experiments Involving the Deliberate Transfer of Recombinant DNA or DNA or RNA Derived from Recombinant DNA into Human Subjects.* This section recapitulates the revised language contained within Section III-C. Additional language has been added to this section stating that RAC members shall notify NIH/ORDA within 15 working days.

Section IV-B-2-a-(3) has been clarified to ensure that all IBCs, in compliance with the *NIH Guidelines,* shall file an *annual* report with NIH/ORDA which includes: (1) a roster of all IBC members clearly indicating the Chair, contact person, Biosafety Officer (if applicable), plant expert (if applicable), animal expert (if applicable), human gene transfer *ad hoc* consultant (as deemed necessary), and (2) biographical sketches of all IBC members (including community members).

Section IV-B-2-b-(1) has been clarified to state that the IBC should ensure compliance with all surveillance, data reporting, and adverse event reporting requirements required by the *NIH Guidelines*. This IBC function becomes particularly important in the face of relinquishing RAC approval of human gene transfer experiments.

Relevant sections of Appendices P and Q have been moved to Sections IV-B-4 and IV-B-5. These sections state that the IBC shall include a plant expert (if applicable) and an animal expert (if applicable). For consistency, a new section, IV-B-6, has been added relevant to institutions conducting or participating in human gene therapy research. Section IV-B-6, *Human Gene Therapy Expert*, states that every institution that participates in or sponsors recombinant DNA research involving human subjects, the institution must ensure that: (1) the IBC has adequate expertise and training (using *ad hoc* consultants as deemed necessary) and (2) all aspects of Appendix M, *Points to Consider*, have been appropriately addressed by the principal investigator prior to submission to NIH/ORDA.

Similarly, Section IV-B-7-b-(6) notes that principal investigators shall ensure that all aspects of Appendix M have been appropriately addressed prior to submission of human gene therapy experiments to NIH/ORDA.

Relating to the NIH Director's responsibilities, Section IV-C-1-a-(4) states that the NIH Director must conduct and support a training program in laboratory safety for IBC members, Biological Safety Officers, other containment experts (if applicable), Principal Investigators, and laboratory staff. A new Section IV-C-1-a-(5) was inserted to state that NIH Director will establish and convene Gene Therapy Policy Conferences (GTPCs) as described in Appendix M.

Relating to the RAC's responsibilities, Section IV-C-2 has been clarified. This section explains that the RAC shall be responsible for: (1) advising the NIH Director on the actions listed in Section IV-C-1-b, *NIH Director--Specific Responsibility;* (2) identifying novel human gene transfer experiments deserving of public discussion by the full RAC; (3) transmitting specific comments/recommendations about a specific human gene transfer experiment or a category of human gene transfer experiments to the NIH Director; (4) publicly reviewing human gene transfer clinical trial data and relevant information evaluated and summarized by NIH/ORDA in accordance with the annual data reporting requirements; and (5) identifying broad scientific and ethical/social issues relevant to gene therapy research as potential GTPC topics. Dr. Smith inquired whether recommendations for GTPC topics should be limited solely to the NIH Director. Ms. Knorr clarified that the RAC officially acts as an advisory to the NIH Director. She emphasized that in addition to the RAC, the NIH Director would seriously take the recommendations of other Federal agencies into consideration.

Dr. Glorioso asked how data reporting information will be reviewed by the RAC. Ms. Knorr explained that data reporting is required annually rather than semiannually, but adverse events should be reported immediately. All safety reports submitted between RAC meetings will be included in the meeting material for the next scheduled RAC meeting. Dr. DeLeon said that if the RAC relinquishes approval of individual gene transfer protocols, it is important to emphasize data reporting requirements.

Relating to NIH/ORDA responsibilities, several modifications were incorporated into Section IV-C. Section IV-C-3-a states that ORDA shall serve as the focal point for public access to summary information pertaining to human gene transfer protocols. Section IV-C-3-d states that ORDA should transmit comments/recommendations arising from public RAC discussion of a novel human gene transfer experiments to the NIH Director. RAC recommendations shall be forwarded to the Principal Investigator, the sponsoring institution, and as appropriate, other Department of Health and Human Services (DHHS) components. Section IV-C-3-e states that ORDA shall collaborate with Principal Investigators, IBCs, IRBs, and other DHHS components (including the FDA and OPRR, to ensure human gene transfer experiment registration compliance in accordance with Appendix M-I, *Submission Requirements, Human Gene Transfer Experiments*. Section IV-C-3-f states that ORDA shall administer the GTPCs. Section IV-C-3-I-(2) states that announcements of GTPCs and tentative agendas will be published in the *Federal Register* at least 15 days in advance of each GTPC. Ms. Meyers remarked that the 15 day notification period should be increased to between 30 and 45 days to encourage broader attendance and sufficient notification.

Ms. Knorr described the changes made in Appendix M, *Points to Consider in the Design and Submission of Protocols for the Transfer of Recombinant DNA Molecules of One or More Human Subjects (Points to Consider)*. The phrase, *into the genome*, has been removed from the title of this appendix since this language does not accurately describe the majority of protocols submitted to date. Responding to Dr. Straus' question regarding proprietary information, Ms. Knorr noted that the preamble to Appendix M states that any application submitted to NIH/ORDA should not be designated as "confidential" in its entirety. In the event that a sponsor determines that specific responses to one or more of the items described in Appendix M should be considered as proprietary or trade secret, each item should be clearly identified as such. Upon submission of a human gene transfer protocol to NIH/ORDA, a cover letter should be attached. This cover letter should: (1) clearly indicate those portions of the application

containing information considered proprietary or trade secret, (2) provide a brief explanation as to the reason that each of these items is determined proprietary or trade secret. Dr. Straus suggested that a reference to this *note* be included in Section I of the *NIH Guidelines* which highlights proprietary information. Ms. Rothenberg and Dr. Lysaught noted a difference in the earlier statement that the submission should contain no proprietary data or trade secret rather than clearly indicate the proprietary data or trade secret.

Appendix M-I, *Submission Requirements--Human Gene Transfer Experiments*, remains essentially unchanged except that the Appendix M page limitations have been eliminated. This modification has been introduced to avoid the timely reformatting of information most likely contained within a subset of the IND application.

Dr. Parkman noted that in several places of the *NIH Guidelines,* the wording "human gene transfer *protocols* or *proposals*" has been changed to "human gene transfer *experiments*." The word "experiment" sometimes has positive and negative connotations. He preferred the more neutral term "protocol" to refer to the organized way of conducting a clinical study.

Appendix M-VI, *RAC Review--Human Gene Transfer Experiments*, states that in order to maintain public access to information regarding human gene transfer protocols, NIH/ORDA will maintain the documentation described in Appendices M-I through M-V (including protocols that are not reviewed by the full RAC). This paragraph contains a statement that the submitted materials contain no proprietary data or trade secrets, enabling all aspects of the discussion to be open to the public.

The last item is Appendix M-VIII-A, *Footnote of Appendix M,* which defines a category of vaccine experiments that are exempt from Appendix M-1, *Submission Requirements*, and Appendix M-VIII, *Reporting Requirements*. If the RAC no longer recommends approval/disapproval of individual gene transfer protocols, the RAC may want to consider deletion of this exemption so that all of the human gene transfer experiments conducted in compliance with the *NIH Guidelines* would be included in the comprehensive relational database currently under development by the NIH/ORDA.

Identification of Discussion Topics

Dr. Walters asked the RAC members to identify specific sections of the *Proposed Actions* requiring further revisions. He noted that the following 13 topics were identified and posed for potential modification: (1) Compliance issues. Dr. Straus indicated his desire to discuss the compliance issue stated in Section IV-D. (2) Issues regarding the GTPCs. Several RAC members suggested a closer coordination between the RAC and GTPCs. (3) Triggering mechanisms and majority vote. Several RAC members have recommended clarification of process by which protocols would be recommended for full RAC review. (4) Informed Consent documents. Dr. Ross stated that a procedure should be developed for review of Informed Consent documents. Ms. Knorr suggested that the Informed Consent documents be reviewed as part of the data management process, and any comments could be relayed to the appropriate IRBs. Dr. Lysaught said that this kind of review would occur after the fact. (5) Feedback mechanisms. Dr. Parkman recommended that the mechanisms by which updated information about a specific protocol is transmitted back to the RAC. The RAC and public should remain informed as to any additional modifications to the originally submitted protocol (including changes that occurred during the FDA IND process). The RAC should be informed about how individual recommendations were addressed or incorporated. (6) Initiation of human gene transfer experiments abroad. Ms. Meyers was concerned that there may be a trend relevant to development of vectors in the United States, which are subsequently transported out of this country for conduct of human gene transfer experiments abroad. Ms. Knorr noted that the guidelines for recombinant DNA research performed abroad is described in Section I-C-1-b. (7) Individual protocol

discussion. Dr. Lysaught proposed to discuss the issue of protocol approval. (8) The endpoint of discussion. Ms. Rothenberg suggested that the parameters for protocol discussion (including scientific merit, safety, and ethical concerns) should be clarified. Dr. Parkman made an observation that from his RAC experience, he was not convinced that summing up the discussion of a protocol in a global approval/disapproval is productive; he believed that recommendations and critiques of a protocol and how they are implemented to modify the protocol are a more important outcome of RAC discussion. (9) Interfacing NIH and FDA submissions. Several RAC members suggested further discussion about the timing of NIH versus FDA submissions and how RAC recommendations will be followed up by the FDA. (10) Identification of GTPC topics. Dr. DeLeon suggested further discussion of the details of this process. (11) Relevance of the footnote in Appendix M regarding vaccine exemptions. Dr. Smith stated that this vaccine footnote should be deleted to enhance public accountability of all human gene transfer research. (12) Proprietary information. Dr. Straus suggested that the issue of proprietary information should be further discussed. (13) Several RAC members recommended that the term "any" should be changed to "all" for those sections of the *NIH Guidelines* pertaining to the requirement for IBC approval prior to submission of a human gene transfer protocol to theNIH/ORDA.

Other Comments

Dr. Noguchi stated that discussion of overarching issues by the RAC will significantly impact FDA policy relevant to gene therapy research. GTPCs will be extremely useful in anticipation of protocol submission representing novel issues, e.g., *in utero* applications.

Dr. Walters asked Dr. Noguchi to clarify the Appendix M submission issue raised in Dr. Andra Miller's letter to the RAC dated November 20, 1996. Specifically: (1) removal of the requirement for submission of Appendix M to the FDA, since the FDA does not accept Appendix M in place of an IND submission, (2) exploring the feasibility of a unified format for submission of protocols to the RAC and the FDA, and (3) establishing a mechanism by which FDA staff could bring general issues of novelty and concern to the RAC for discussion. Dr. Parkman was concerned that removal of the requirement for submission of Appendix M may be interpreted by some investigators that they no longer need to respond to Appendix M of the *NIH Guidelines*. Dr. Noguchi responded that Appendix M is only a subset of an FDA IND submission. FDA does not require the sponsor to submit Appendix M. Dual submission causes confusion for sponsors; Appendix M is not an official FDA document. Dr. Parkman stated any single submission format should include those portions of Appendix M that are not specifically addressed by IND requirements.

VI. PUBLIC COMMENTS

Dr. Walters requested public comments.

Mr. Steven Kradjian, Vical, Inc. (San Diego, CA), asked for clarification regarding: (1) the proposed requirements for IBC and IRB approvals prior to submission to the NIH; and (2) whether the IBC is required to periodically review a protocol to ensure the reporting requirements required by the *NIH Guidelines*.

Ms. Bridget Binko, Cell Genesys (Foster City, CA), suggested that RAC review of novel protocols should occur well in advance of development of the final protocol (similar to the FDA's pre-IND review process) rather than at the final stage of protocol development. Dr. Parkman asked if the submission of Appendix M to NIH/ORDA could be independent of FDA IND submission. Dr. Noguchi supported early submission of Appendix M to NIH/ORDA at the pre-IND stage.

Dr. Diane Fleming (Biosafety Consultant, Maryland) suggested that: (1) NIH should convene an IBC Chairperson Conference, and (2) development of IBC Guidelines.

Ms. Tina Grasso, GenVec (Rockville, Maryland), inquired if minimal information (without full submission) would provide adequate information by which the RAC could make its decision regarding necessity for full RAC discussion. Dr. Parkman was concerned that such an incomplete submission would not be sufficient to evaluate whether a protocol is truly novel, e.g., incomplete vector information. Dr. Lysaught remarked that investigators' responses to Appendix M-II, *Description of the Proposal*, are useful to the public RAC members to adequately evaluate each protocol. Dr. Smith asked about the extent to which Appendix M-II overlaps with an IND submission. Ms. Meyers stated that it would be preferable to have a unified NIH and FDA submission format. Ms. Knorr responded that she has had ongoing discussions with FDA staff about implementation of such a unified format. It is anticipated that these productive lines of communication will be continued, and that a unified format can be developed that is mutually acceptable to each agency.

VII. CHAIR REMARKS

Dr. Walters presented certificates and plaques to the outgoing RAC members: (1) Dr. Arno G. Motulsky, University of Washington, Seattle, Washington, (2) Dr. Brian R. Smith, Yale University, New Haven, Connecticut, (3) Dr. Stephen E. Straus, National Institutes of Health, Bethesda, Maryland, (4) Dr. Marian G. Secundy, Howard University, Washington, D.C., and (5) Ms. Abbey S. Meyers, National Organization for Rare Disorders, New Fairfield, Connecticut. He thanked them for their dedication to the field of human gene therapy and having completed their term of service on the RAC in an exemplary manner.

Dr. Walters noted a TMC Worldwide Gene Therapy Enrollment Report provided by Dr. Tony Marcel, TMC Development, Paris, France.

Dr. Walters asked for further discussion and a committee vote on the topics put on the table.

VIII. CONTINUED RAC DISCUSSION OF *PROPOSED ACTIONS*

Future RAC Membership

Ms. Meyers asked if the NIH Director intends to appoint new RAC members. Ms. Knorr responded that she anticipates that new members will be appointed by the NIH Director in the very near future. Ms. Rothenberg emphasized the importance of "maintaining the RAC's institutional memory" and expertise. She suggested that to ensure such continuity, several former RAC members should be invited back as *ad hoc* consultants through this significant transition period.

Committee Motion 1

A motion was made by Ms. Rothenberg and seconded by Dr. Ross to invite former RAC members back to serve as *ad hoc* consultants in order to ensure institutional memory and continuity of RAC discussions. The motion passed by a vote of 15 in favor, 0 opposed, and no abstentions.

Dr. Ross was concerned that the RAC does not have sufficient time to complete discussion of all the topics on the table. Dr. Motulsky asked if a mail vote could be taken for the remainder of the subjects. Ms. Knorr noted that the Federal Advisory Committee Act requires that any vote taken on the *Proposed Actions* which were published in the *Federal Register* must occur during this public meeting. Dr. Hirschhorn remarked that the topics on the table need to be discussed thoroughly before a vote can be

taken. Dr. Noguchi agreed that any vote on these public policy issues must occur in public. Dr. Walters suggested that a subcommittee should be formed to address those topics in which the RAC has not come to closure on during today's meeting.

Dr. Walters noted 5 remaining topics for today's discussion: (1) coordination of the RAC and theGTPC, (2) identification of the triggering mechanisms for requiring full RAC discussion of an individual protocol, (3) developing feedback mechanisms after RAC discussion of protocols, (4) absence of procedures for reviewing Informed Consent documents, and (5) issues regarding the endpoint of RAC protocol discussion.

Triggering Mechanisms for RAC Discussion

Dr. Parkman proposed that principal investigators and institutional representatives should not be allowed to request public RAC discussion of an individual protocol to avoid the possibility that the RAC might be used as a public relations platform. He recommended limiting recommendations for protocol review to the RAC, the NIH Director, and the FDA, thereby eliminating the necessity for theNIH Director to set the agenda for such discussions.

With regard to the *majority* requirement for RAC recommendation of protocol review, Dr. Parkman suggested that the number of recommending RAC members should be reduced to four members. Dr. Straus noted that in development of such a recommendation, the committee must be sensitive to the public members who are a minority of the RAC and whose views on individual protocols are important. The rationale for RAC discussion of an individual protocol should be considered, rather than a majority vote. Dr. Straus suggested that the rationale for requesting RAC review be circulated among RAC members, and that final recommendations should be made after careful consideration of the individual issues raised by each member. Dr. Parkman agreed with Dr. Straus' comments. Dr. Ross asked if summary sheets will be circulated to all RAC members. Ms. Knorr responded that summary information of protocols will be faxed to all RAC members and, upon request, the complete submission will be sent by overnight delivery.

Dr. Parkman made a motion that protocol summary information should be circulated to all RAC members, and that the trigger for full RAC discussion would be a recommendation for full RAC review by a minimum of four RAC members at the end of the 15 day review period. Dr. Smith seconded the motion.

Dr. Motulsky inquired if the exempt decision has to be made within 15 working days. Dr. Parkman said that the RAC's decision to recommend protocol review should be made when possible within the 15 day period, or perhaps, within 30 days to be consistent with current FDA regulations.

Ms. Rothenberg suggested that the trigger for RAC review should be two RAC members instead of four RAC members. Dr. Parkman remarked that if a RAC member identifies a truly substantive issue there should be ample justification to convince an additional three members of the necessity for full RAC review. Dr. Smith agreed that a recommendation for full RAC review by four or more RAC members is a sufficient trigger, provided that initial RAC comments are circulated to all other reviewers for consideration. Ms. Knorr agreed to immediately circulate comments submitted by each RAC member who recommends full review. Dr. Motulsky expressed his support for the motion. Ms.Knorr said that the timeframe of 15 working days is reasonable allowing 10 days for the initial round of circulation and 5 more days for a final decision. Ms. Rothenberg suggested that a cautious way to proceed would be to use the lower threshold of two votes, gradually increasing the number of required votes as public confidence is gained. Ms. Meyers suggested a friendly amendment to require a compromise of three votes. Dr. Parkman and Ms. Rothenberg accepted the friendly amendment.

Committee Motion 2

A motion was made by Dr. Parkman and seconded by Dr. Smith that: (1) the capacity for principal investigators and institutional representatives to request public RAC discussion of an individual gene transfer protocol should be deleted; (2) a decision by the RAC to require full review of an individual protocol should not have to be approved by the NIH Director; (3) the NIH Director or an appropriate FDA representative may request RAC review of an individual protocol; (4) rather than a majority vote, the triggering mechanism for full review of an individual protocol will be changed to a minimum of three members; (5) whenever possible, the decision regarding necessity for RAC discussion should be made within 15 working days. The motion passed by a vote of 16 in favor, 0 opposed, and no abstentions.

The Feedback Mechanism

Dr. Parkman asked Dr. Noguchi to what extent the FDA would be permitted to transmit information about its final actions on a specific gene transfer protocol that could be provided to the RAC and the NIH. Dr. Noguchi responded that summary information, such as FDA implementation of specific recommendations made by the RAC regarding a specific protocol, could be provided by the FDA to the RAC. He did not specify further the types and amount of information that could be publicly disclosed.

Dr. Parkman made a motion to require that the FDA report back to the RAC regarding FDA actions on RAC recommendations resulting from RAC discussion of individual protocols. If the FDA information is inadequate, investigators could be asked to provide additional information. Dr. Zallen seconded the motion.

Dr. Straus asked Dr. Noguchi if the FDA has the authority to publicly disclose such information. Dr. Noguchi said that the official FDA response to an IND application is a written letter stating that the sponsor may: (1) proceed without further review, (2) proceed pending submission of additional information within a specified time-frame, or (3) not proceed (clinical hold) until IND deficiencies are adequately addressed. Dr. Noguchi noted that FDA permission to proceed is always dependent upon receipt of final IRB approval. Dr. Noguchi emphasized that such documentation cannot be disclosed by the FDA. Dr. Straus asked if the RAC members could have access to such documents. Dr. Noguchi responded that as special government employees, RAC members could have access to such information but are bound by the same rules of confidentiality as FDA employees. Dr. Parkman asked if the FDA could provide a summary of how investigators respond to RAC recommendations and any modifications made to the protocol during the FDA IND approval process.

Dr. Straus stated that as an NIH committee, the RAC is unable to require the FDA to provide such information to the NIH; however, the RAC is empowered to require investigators to provide information regarding how their protocols are modified after FDA review. Dr. Straus stated his opposition to Dr. Parkman's motion. Ms. Knorr added that a statement could be inserted to Section M-VII, *Reporting Requirements--Human Gene Transfer Protocols*, to require investigators to report back to the RAC the full details of how RAC recommendations are implemented after FDA IND approval is obtained.

Dr. Lysaught noted the timing issue of RAC review versus FDA review. Protocols could be approved by FDA before RAC discussion. Dr. Noguchi said that he supports separation of Appendix M from the FDA submission, partly for this reason; FDA has to respond to an IND submission within 30 days. Dr. Chase said that it will be more useful if the RAC focuses on those truly novel experiments rather than trying to deal with every protocol. Dr. Ross stated that she shares Dr.Lysaught's concern about the timing issue. Ms. Rothenberg pointed out that it is within FDA's authority to hold its decision regarding a protocol until

after a RAC discussion; otherwise, RAC review could occur after an investigator has received permission to proceed by the FDA. Dr. Noguchi responded that the FDA is not willing and is unable to change its rules regarding the 30 day IND deadline or to require RAC approval of a protocol prior to FDA permission to proceed. Ms. Rothenberg asked why FDA would ever ask the RAC to review a novel protocol if they are bound by this 30 day limit. Dr. Noguchi said that the RAC is most useful in discussing the protocol at the pre-IND stage; the investigators and the sponsors will have the feedback from the RAC and the public to decide if they should submit their IND to the FDA. FDA does not want to adopt a special review procedure for gene therapy protocols. Dr. Smith asked for clarification of the *Proposed Actions.* If RAC recommends full review of a gene transfer protocol, would the investigator be required to postpone initiation of the clinical trial pending full RAC review? Ms. Knorr responded that the *Proposed Actions* are not intended to delay initiation of such trials. It is assumed the de facto review of a novel application will still yield information that will impact development of future trials and ensure public accountability. Ms. Knorr suggested that the RAC may want to consider the earlier suggestion presented by Ms. Bridget Binko, Cell Genesys, San Diego, California. Specifically, RAC consideration of human gene transfer protocols at the pre-IND stage of protocol development. RAC's recommendations would be weighed with greater significance. At the pre-IND stage, the experimental study design is still under development.

Dr. Straus responded that the RAC should not have to review a protocol that is still under development. Dr. Straus said that review of a protocol after FDA approval would still have influence on several aspects including guidance for future actions by the FDA. The RAC can influence the protocol through its reporting and compliance requirements under the *NIH Guidelines*.

Ms. Meyers was concerned that FDA might approve protocols without adequate consideration of ethical issues, e.g., proposals for enhancement gene therapy. Dr. Smith called Dr. Parkman's motion for a vote. Dr. Hirschhorn agreed to call Dr. Parkman's motion for a vote.

Committee Motion 3

A motion was made by Dr. Parkman and seconded by Dr. Zallen to request that the FDA report back to the RAC how its recommendations on an individual protocol are implemented. The motion failed by a vote of 3 in favor, 7 opposed, and 4 abstentions.

A motion was made by Dr. Straus and seconded by Dr. Smith to require investigators to provide a report to the RAC, in writing, in a timely fashion, that specifies how individual RAC recommendations were responded to and any modifications that were made to the protocol either during the course of or following FDA IND approval. Dr. Lysaught made a friendly amendment to include this requirement as part of the reporting requirements stipulated by the *NIH Guidelines*. Dr. Straus accepted the friendly amendment. Dr. Chase said the follow-up discussion of a protocol is an useful exercise for the RAC. Dr. Straus said that this follow-up reporting should be applicable to all protocols registered with NIH/ORDA, not just those that are discussed publicly by the RAC. Dr. Walters stated that this motion should focus on the feedback information regarding those protocols that receive full RAC discussion. Dr. Straus agreed; he pointed out that when the RAC discusses the feedback reporting at the RAC meetings, patients could already have been enrolled in these protocols. Dr. Hirschhorn said that IRBs usually condition their final approval of protocols upon receipt of FDA IND approval.

Committee Motion 4

A motion was made by Dr. Straus and seconded by Dr. Smith to require investigators to report back to the RAC in writing in a timely fashion for the protocols that receive full RAC discussion. The report should include a statement of how the investigators have responded to RAC recommendations and any

modifications to the protocol following FDA review. The motion passed by a vote of 12 in favor, 1 opposed, and 1 abstention.

The approval issue was briefly discussed. Drs. Ross and Smith said that the approval issue is important and needs to be discussed more fully. Dr. Glorioso said that if the RAC's responsibility is not clarified, he would favor disbanding the RAC. Dr. Chase noted that the RAC already has relinquished its responsibility of full review of most of the protocols to FDA under the NIH/FDA consolidated review process. Ms. Rothenberg stated that absent approval authority, the significance of RAC discussion of novel protocols will be diminished. Dr. Ross stated that RAC approval of novel protocols is important; the primary focus of the RAC approval is public safety and consideration of significant ethical issues.

Dr. Walters reminded the RAC about a recommendation adopted by the RAC at its December 4-5, 1995, meeting by a vote of 16 in favor, 0 opposed, and no abstentions. The motions states, "The RAC should continue to function under *status quo*, i.e., selective review and approval of novel human gene transfer protocols." The resolution of the RAC was apparently not accepted by the NIH Director, and this scenario has led to the present *Proposed Actions*. Dr. Chase agreed that further discussion of the approval issue is a moot point; the RAC should focus on finding an effective way to use its moral persuasion to appraise gene transfer protocols and to obtain valuable knowledge that will continue to advance this unique field of biomedical research in a safe and ethical manner.

Relationship of the RAC and GTPC

Dr. Glorioso stated that the RAC should take the lead in establishing policy for the conduct of future gene therapy research such as formulating guidance for the use of novel vectors. The RAC should be proactive to future issues rather than reactive to submitted protocols. The GTPC will be an useful forum for the RAC to develop policy for future gene therapy research. Dr. Chase agreed.

Ms. Knorr noted that another major function of the RAC is to review the field through the annual data reporting process. Dr. Hirschhorn stated that the data reporting is public accountability of gene therapy research. Much can be accomplished if the RAC continues to keep abreast of preliminary and published results. Dr. Hirschhorn said that RAC needs to focus on the most effective mechanisms to accomplish this objective. Ms. Meyers noted that from her perusal of data reportings in the past, she found that most protocols have failed to request autopsies, and the RAC lacks an effective mechanism to correct this situation. Dr. Noguchi said that FDA has oversight of commercial IRBs that are outside OPRR purview. He reminded the RAC that the approval authority of protocols has been delegated to FDA under the *Coordinated Framework for Regulation of Biotechnology* published in *Federal Register* on June 26, 1986 (51 FR 23302). Dr. Noguchi expressed support for Dr. Glorioso's proposal to convene the GTPCs to discuss novel policy issues well in advance of actual protocol development, e.g., *in utero* gene therapy.

Ms. Rothenberg stated that in order for the RAC to have a meaningful existence, the RAC should be able to exert its influence on policy development by planning the GTPC agenda, not just to suggest conference topics.

Dr. Straus stated that the approval issue should be no longer debated. The RAC should provide a public forum for discussion of gene therapy policy and provide in-depth analysis of both preliminary and published data irrespective of whether the NIH Director retains approval authority of individual protocols. Dr. DeLeon supported Dr. Straus' statement that the RAC should use its data management process to help form policy, and that the RAC should have an integral relationship with GTPCs. Dr. Chase said that expert discussion of the data reporting would have a powerful influence on the field and expressed his support of the proposal.

Dr. Walters asked the RAC to introduce a motion regarding the GTPCs and suggested that a subcommittee should be formed to consider the remaining issues. Dr. Lysaught asked if a special meeting could be convened before the next RAC meeting. Ms. Knorr responded that it is necessary to allow for adequate notification of such a meeting; therefore, scheduling of an additional meeting before the March RAC meeting is probably not a feasible option.

Dr. Glorioso made a motion that the RAC should host GTPCs, rather than just have a member co-chair each conference. The RAC should play a proactive role in organizing GTPCs and adopt this responsibility as a primary RAC function. Dr. Zallen seconded the motion. Dr. Straus asked if the GTPCs may be initiated by other parties outside the RAC. Dr. Glorioso responded that the RAC should initiate the first GTPC, demonstrating its leadership role. The RAC should prioritize the most urgent policy issues, e.g., new vectors, new kinds of therapy, etc. Other entities can propose conference topics, but the RAC should retain the primary responsibility for setting GTPC agendas and organizing their participants. Ms. Knorr noted that the GTPCs can occur simultaneously with the RAC meetings.

Dr. Smith stated that the RAC should summarize the conclusions and recommendations of each GTPC and develop specific policy recommendations to the NIH Director. He recommended that RAC meetings should be held immediately following the conclusion of GTPCs. Drs. DeLeon and Ross agreed that the RAC should summarize the results of the GTPC and make policy recommendation to the NIH Director. Dr. Ross noted that review of specific novel protocols could help identify potential topics for future GTPCs. Dr. Smith emphasized that the RAC should entertain a motion and vote on the entire *Proposed Actions* proposed by Dr. Varmus.

Ms. Rothenberg stated that the close relationship of the RAC to the GTPCs is different than the process that is outlined in the *Proposed Actions* and expressed her support for such a modification. Drs. Straus and Zallen expressed their support for holding GTPCs in conjunction with RAC meetings, preferably having the GTPC on the first day, with the RAC meeting held on the second day to discuss the outcome o the GTPC and to make policy recommendations.

Dr. Motulsky noted that as originally proposed, the GTPC would include concentrated discussion of scientific issues, which may not have immediate public interest. Discussion of novel scientific thoughts such as details of virology, other vectors, and manifestation of diseases might lead to a better way of conducting gene therapy research, but such discussions may not have an immediate impact on the public policy. For this reason, the two entities should remain separate. Dr. Hirschhorn said that Dr. Varmus originally envisioned the GTPC as a workshop for novel gene therapy issues. It is preferable that the GTPCs, are coincident with the RAC meeting. Dr. Walters noted that there seems to be a consensus among the RAC members to convene quarterly RAC meetings in conjunction with GTPCs. Dr. Walters stated that even in the course of scientific discussions, policy issues could emerge. Dr. Glorioso noted that Dr. Walters' remark is compatible with his motion.

Dr. Motulsky said that he still prefers that GTPC not be formally linked to the RAC meeting because in some occasions the GTPC does not fit into the RAC's usual agenda. GTPCs should be considered meetings involving participants with concentrated expertise in which the RAC members can participate. Dr. Straus agreed with Dr. Motulsky. Ms. Knorr noted that the GTPC could be advisory to the NIH Director, rather than to the RAC.

Dr. Walters offered an opportunity for the public to comment on this issue. Dr. Gerard McGarrity, Genetic Therapy, Inc., Gaithersburg, Maryland, suggested that it is important to retain flexibility during the initial planning stages of the relationship between the RAC and GTPCs.

Dr. Glorioso summarized his motion stating that the RAC should take primary responsibility for planning GTPC agendas and summarizing the recommendations from the GTPC in a report back to the NIH Director.

Dr. Smith made a friendly amendment to the motion that the close relationship of the RAC and the GTPC does not exclude other parties from suggesting GTPC topics. Drs. Glorioso and Zallen accepted Dr. Smith's friendly amendment. Ms. Rothenberg proposed a friendly amendment that the RAC should recommend and convene GTPCs in consultation with the FDA. Dr. Noguchi agreed. To maintain flexibility, Dr. Glorioso suggested that it should not be mandatory for GTPCs to be held in conjunction with the RAC meetings. Ms. Rothenberg noted that if the goal of the GTPCs is to generate policy discussion when deemed appropriate, GTPCs should be held in conjunction with the RAC meeting.

Committee Motion 5

A motion was made by Dr. Glorioso and seconded by Dr. Zallen that the RAC, with the NIH Director's approval, should have the primary responsibility for: (1) planning GTPC agendas, and (2) summarizing GTPC recommendations in the form of a report back to the NIH Director. The close GTPC/RAC relationship should not preclude other parties from suggesting GTPC topics, and the GTPCs should be convened in consultation with FDA. The motion passed by a vote of 13 in favor, 0 opposed, and 2 abstentions.

Proposed Actions Concepts

Dr. Walters listed the remaining discussion topics and suggested that a subcommittee should be formed to work on these issues. Dr. Chase said that the RAC should formulate a response to the Director's proposal. Dr. Chase explained the reason that he abstained from voting for Committee Motion 5 is because of his reservation about the RAC taking the primary responsibility for planning the GTPC agendas. As an advisory committee to the NIH Director, the RAC should respond to and provide advice upon request from the NIH Director, rather than stipulate its agenda to the NIH Director. Dr. Smith noted Section III-B of the *Proposed Actions* listed several functions of the RAC. Ms. Knorr explained that most of these functions have been always within the RAC's purview. Dr. Chase recommended that the remaining issues not be resolved during today's meeting should be deferred to a future time.

Ms. Knorr emphasized that the RAC should vote on the *Proposed Actions* in its entirety today. Ms. Rothenberg inquired if the NIH Director can unilaterally take action if the RAC does not vote on these *Proposed Actions.* Ms. Knorr encouraged the RAC to vote on the overall structural changes proposed by the NIH Director. Ms. Rothenberg said that the RAC already voted on several motions today, the rest of the issues could be resolved at the March 1997 RAC meeting. Dr. Straus shared Ms. Rothenberg's concern and said that although he was pleased with the proposal, there are still many important issues that have not been resolved. Dr. Lysaught agreed with Dr. Straus.

Ms. Rothenberg highlighted the timing issue relevant to NIH and FDA submissions. This issue will require more detailed discussion at the March 1997 RAC meeting. She suggested that the NIH Director provide feedback to the RAC in response to the major concerns raised during the course of today's discussion of these *Proposed Actions*.

Ms. Knorr emphasized that the RAC should vote on the five overall structural changes proposed by the NIH Director in the *Proposed Actions*. These five proposals are: (1) retain the RAC, while modifying its roles and responsibilities relevant to human gene therapy research; (2) continue RAC *discussion* of novel

human gene transfer experiments without RAC *approval* of individual human gene transfer experiments; (3) reduce the membership of RAC from 25 members to 15 members; (4) regularly convene GTPCs; and (5) maintain public access to human gene transfer clinical trial information. The remaining minor issues could be addressed at some future point. She emphasized the importance of sending a positive message about these *Proposed Actions* to the NIH Director. Dr. Straus agreed with Ms. Knorr stating that he supports the five major points of the proposal; however, there are some details that need further discussion. Dr. Chase stated that Dr. Varmus has made a good faith effort to respond to the concerns of the RAC and the public. Dr. Chase endorsed the overall principles set for the *Proposed Actions*. Because of the shortage of time, some details of the proposal need further discussion. Dr. DeLeon and Ms. Rothenberg agreed with Dr. Chase, but Ms. Rothenberg noted her continued concern about the feasibility of discussing novel human gene transfer experiments in the absence of approval. Ms. Knorr suggested the RAC could accept the overall structural changes with incorporation of the modifications that have been voted on today. Dr. Walters summarized the consensus of the discussion stating that the RAC approves the five overall concepts put forward in the *Proposed Actions;* however, the consensus of the committee is that more time is needed to discuss the remaining issues prior to implementation of the proposed structural changes.

Committee Motion 6

A motion was made by Dr. Straus and seconded by Dr. Lysaught to accept the overall concepts put forward in the *Proposed Actions* as published in November 22, 1996, *Federal Register* (61 FR 59725). Specifically: (1) retain the RAC, while modifying its roles and responsibilities relevant to human gene therapy research; (2) continue RAC *discussion* of novel human gene transfer experiments without RAC *approval* of individual human gene transfer experiments; (3) reduce the membership of RAC from 25 members to 15 members; (4) regularly convene GTPCs; and (5) maintain public access to human gene transfer clinical trial information. The members of the RAC noted that several minor modifications still remain unresolved, particularly with regard to future discussion of gene therapy protocols and defining the role of the RAC relative to GTPCs.

The RAC recommended that final action on the *Proposed Actions* should be postponed until after the March 6-7, 1997, RAC meeting, in order to more fully address these unresolved issues. The motion passed by a vote of 12 in favor, 0 opposed, and 2 abstentions.

IX. DATA MANAGEMENT

Dr. Smith provided a brief data management overview of information submitted to ORDA since the December 4-5, 1995, RAC meeting. A total of 27 protocols have been submitted since December 1995. A total of 167 human gene transfer protocols have been submitted to NIH/ORDA to date.

Of the human gene transfer protocol safety reports submitted since the December 4-5, 1996, most advers events should be considered to be directly related to complications of underlying disease and not to the gene transfer aspects of these protocols.

(1) Complications were reported for Protocol #9502-099, related to stereotactic brain surgery in the HSV-TK/glioblastoma protocol, i.e., hematoma, edema, and necrosis.

(2) Neutropenia and zoster following stem-cell transplant were reported for #9306-044.

(3) Increased cholestasis and bacteremia in Fanconi's anemia #9406-078.

(4) Questionable new events were reported for: (a) #9403-069-progressive multi focal leukoencephalopathy in two patients with HIV receiving gene-modified syngeneic cytotoxic T lymphocytes, (b) #9502-099-acute neurologic deterioration of uncertain cause (this may have been due to ganciclovir) in one patient, and (c) #9303-038-myocarditis following transplantation of Epstein-Barr virus specific cytotoxic T lymphocytes.

Increasing variability has been observed in the "quality" of submissions, i.e., failure to comply with Appendix M-I, *Human Gene Transfer Protocols-Submission Requirements,* of the *NIH Guidelines*. Listed below are the number of protocols submitted since December 1995 that did not include the required documentation:

(1)	IRB/IBC Approval	20
(2)	Points to Consider	17
(3)	Scientific Abstract	19
(4)	Non-Technical Abstract	18
(5)	Informed Consent document	25
(6)	Clinical Protocol	27
(7)	Curriculum vitae of Principal Investigators	18
(8)	Vector Sequence Disk	10
(9)	Nucleotide Sequence Analysis	10
(10)	Restriction Map	8

of gene transfer protocols have been submitted since the December 1995 RAC meeting:

(1)	Gene Marking	1
(2)	Gene Therapy	26
(3)	Monogenic Disease (X-linked SCID)	1
(4)	HIV-intracellular replication inhibition	3
(5)	Cancer/Immunotherapy	22
(6)	Cancer/Chemoprotection (MDR-1)	1
(7)	Cancer/Pro-drug (HSV-TK)	7
(8)	Cancer/Tumor suppressor gene Retinoblastoma (1), BCRA1 (1), and E1A (1)	3

vectors have been proposed for human gene transfer protocols submitted since December 1995 RAC meeting:

(1)	Adenovirus	6
(2)	Retrovirus	12
(3)	Liposome/plasmid	5
(4)	Particle Mediated	1
(5)	Vaccinia	2
(6)	Fowlpox	1

A total of 24 protocols were registered with NIH/ORDA and determined to be exempt from full RAC review. Included in these 24 protocols were:

(1) One protocol involving a new gene for a new monogenic disorder (IL2 receptor gamma chain gene for X-linked SCID) (#9604-152).

(2) Two protocols involving new HIV replication inhibitor constructs (#9512-141 and #9602-147).

(3) Two protocols involving new immunotherapy target genes (melanoma antigens) (#9512-140 and #9604-151).

(4) One protocol involving a new tumor suppressor gene (BRCA-1 for breast cancer) (#9603-149).

A total of 3 protocols were forwarded to RAC members for evaluation regarding necessity for RAC review:

(1) Protocol #9601-145 (Principal Investigators: Eric J. Small and Peter R. Carroll). This protocol uses retinoblastoma (Rb) gene as a tumor suppressor gene for bladder cancer. RAC reviewers unanimously agreed that the protocol was exempt from full RAC review (Reviewers: McGraw, Ginsburg, and Saha).

(2) Protocol #9602-147 (Principal Investigator: Donald B. Kohn). This protocol uses an HIV replication inhibitor in pediatric patients. Dr. Lysaught questioned the advisability of using children as research subjects. This protocol was determined to be exempt from full RAC review (Reviewers: Lysaught, Erickson, and Robinson).

(3) Protocol #9610-162 (Principal Investigators: Suzanne LaFollette and James L. Murray). This protocol uses intratumoral injection of E1A as a tumor suppressor gene in those patients whose tumors over express the HER2/neu oncogene. The RAC members were split on the issue of the necessity for full RAC review. This split decision was in part based on previous concerns raised during RAC's discussion of the Hortobagyi protocol (#9512-137), regarding the true nature of the E1A gene (oncogene versus tumor suppressor gene) and the lack of any follow-up data from that protocol (#9512-137). This protocol was determined to be exempt by three scientific RAC reviewers (Smith, Motulsky, and Straus) (Reviewers: Chase, Secundy, Lysaught, Meyers, Zallen, Straus, Smith, Samulski, Motulsky, Ross, and Miller). The Hortobagyi protocol was reviewed at the December 1995, RAC meeting. The final motion recommended approval by a vote of 11 in favor, 5 opposed, and no abstentions.

Other Comments

Dr. Smith noted that Targeted Genetics Corporation, Seattle, Washington, provided a written response dated December 3, 1996, to concerns raised by RAC members regarding Protocol #9610-162. Dr. Smith stated that most of the issues raised by the RAC were satisfactorily answered, i.e., oncogene versus tumor suppressor gene and the follow up data of 3 patients treated in Hortobagyi protocol (#9512-137).

Dr. Zallen noted that several public RAC members recommended full RAC review of Protocol #9610-162. She recalled that the original Informed Consent document of the Hortobagyi protocol was very inadequate, but the revised document was excellent, a model gene therapy Informed Consent document. Dr. Zallen noted that the Informed Consent document for Protocol #9610-162 was the same as the original unsatisfactory document submitted for the Hortobagyi protocol.

Dr. Straus said that when the new RAC review procedures are implemented, the RAC will continue to

face the same dilemma noted by Dr. Zallen, i.e., a protocol may have recruited patients before the RAC review. Dr. Straus suggested that the RAC forward its concerns regarding the protocols and Informed Consent documents to the FDA and local IRBs. IRBs could address these concerns during their annual review.

Ms. Meyers noted that all of 27 protocols submitted since the December 1995 RAC meeting were exempted from full RAC review; she found that most of the submissions were incomplete. Ms. Knorr noted that NIH/ORDA is currently developing a relational database that includes IBC and IRB contacts to facilitate communication and ensure compliance with the *NIH Guidelines*.

Dr. Walters remarked that the past year was an extraordinary period based on uncertainty about the future role of the RAC. Nothing that was administered in the past year relevant to NIH submission and review of gene therapy protocols will serve as a precedent for future protocol submissions.

Dr. Lysaught made a comment regarding the exempt letter dated February 8, 1996, from ORDA to Dr. Donald Kohn of Protocol #9602-147 involving HIV-infected children as research subjects. In her initial review, Dr. Lysaught expressed concern about the advisability of using the pediatric patients as research subjects. Two scientific reviewers recommended that the protocol should be exempt from RAC review. One of the reviewers noted that the local IRB had dealt adequately and responsively with the issue of research subjects' ages and entry into the protocol. Dr. Lysaught stated that she informed NIH/ORDA at that time that she was not inclined to change her mind regarding this protocol.

Dr. Ross stated that she will prepare a list of deficiencies she found in the Informed Consent documents and requested that ORDA contact the relevant investigators and IRBs. Ms. Meyers concurred with Dr. Ross. Ms. Knorr stated that the last year has been an uncertain period for the RAC; many investigators have failed to comply with the *NIH Guidelines*. Ms. Knorr suggested that the RAC address this issue of non-compliance. Dr. Noguchi commented that the IRB has final authority to approve Informed Consent documents; inconsistencies may reflect differences in patient populations. Dr. Chase said that the investigators should be required to provide any missing documentation. Dr. Straus noted that NIH and FDA submission requirements are not identical. Dr. Noguchi said that FDA receives complete IND submissions of the protocols registered with NIH. Ms. Rothenberg recommended that NIH/ORDA should insist that investigators comply with current submission requirements. Ms. Meyers inquired if the FDA has approved the protocols using fowlpox and vaccinia viruses. Dr. Noguchi responded that he would have to consult with FDA records.

Dr. Walters commended the RAC for its constructive work during today's meeting and thanked the RAC members for their efforts.

X. FUTURE MEETING DATES

Dr. Walters announced that the next meeting of the RAC will be March 6-7, 1997, Building 31C, Conference Room 10, NIH.

XI. ADJOURNMENT

Dr. Walters adjourned the meeting at 4:30 p.m. on December 9, 1996.

Debra W. Knorr
Executive Secretary

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

Date: March 6, 1997

C. Estuardo Aguilar-Cordova, Ph.D.
Acting Chair
Recombinant DNA Advisory Committee
National Institutes of Health