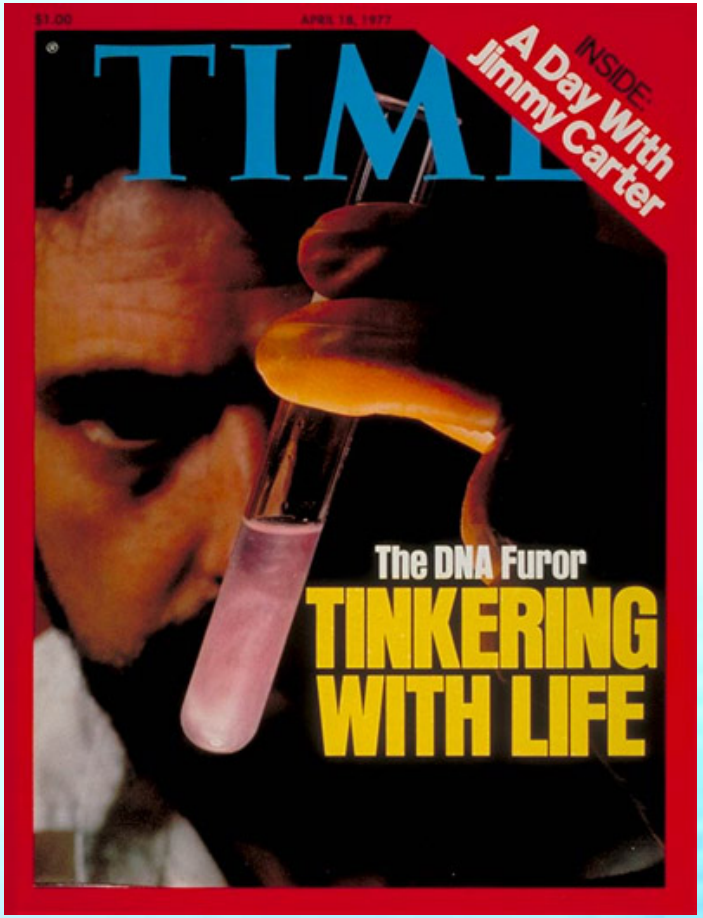
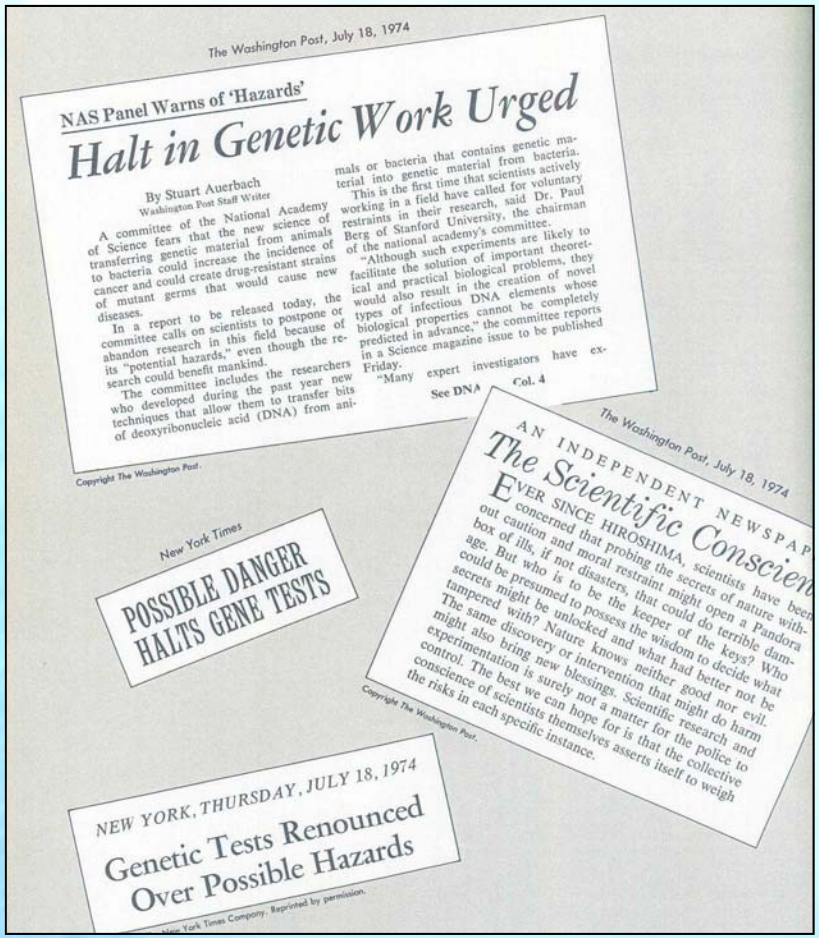
Overview of the Policy and Biosafety Framework for Human Gene Transfer Research: *The NIH Guidelines for Research Involving Recombinant DNA Molecules*

The Advent of Recombinant DNA Technology

- Emergence of recombinant DNA technology (mid-1970's)
- Concerns among both scientific community and general public
  - Public health and safety
  - Environmental impact
  - Potential ethical and social implications



Policy Debate



The Washington Post, July 18, 1974

NAS Panel Warns of 'Hazards'

Halt in Genetic Work Urged

By Stuart Auerbach
Washington Post Staff Writer

A committee of the National Academy of Science fears that the new science of transferring genetic material from animals to bacteria could increase the incidence of cancer and could create drug-resistant strains of mutant germs that would cause new diseases.

In a report to be released today, the committee calls on scientists to postpone or abandon research in this field because of its "potential hazards," even though the research could benefit mankind.

The committee includes the researchers who developed during the past year new techniques that allow them to transfer bits of deoxyribonucleic acid (DNA) from animals or bacteria that contains genetic material into genetic material from bacteria.

This is the first time that scientists actively working in a field have called for voluntary restraints in their research, said Dr. Paul Berg of Stanford University, the chairman of the national academy's committee.

"Although such experiments are likely to facilitate the solution of important theoretical and practical biological problems, they would also result in the creation of novel types of infectious DNA elements whose biological properties cannot be completely predicted in advance," the committee reports in a Science magazine issue to be published Friday.

"Many expert investigators have ex-

See DNA Col. 4

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The Washington Post, July 18, 1974

AN INDEPENDENT NEWSPAP

The Scientific Conscien

EVER SINCE HIROSHIMA, scientists have been concerned that probing the secrets of nature without caution and moral restraint might open a Pandora box of ills, if not disasters, that could do terrible damage. But who is to be the keeper of the keys? Who could be presumed to possess the wisdom to decide what secrets might be unlocked and what had better not be tampered with? Nature knows neither good nor evil. The same discovery or intervention that might do harm might also bring new blessings. Scientific research and experimentation is surely not a matter for the police to control. The best we can hope for is that the collective conscience of scientists themselves asserts itself to weigh the risks in each specific instance.

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New York Times

POSSIBLE DANGER HALTS GENE TESTS

NEW YORK, THURSDAY, JULY 18, 1974

Genetic Tests Renounced Over Possible Hazards

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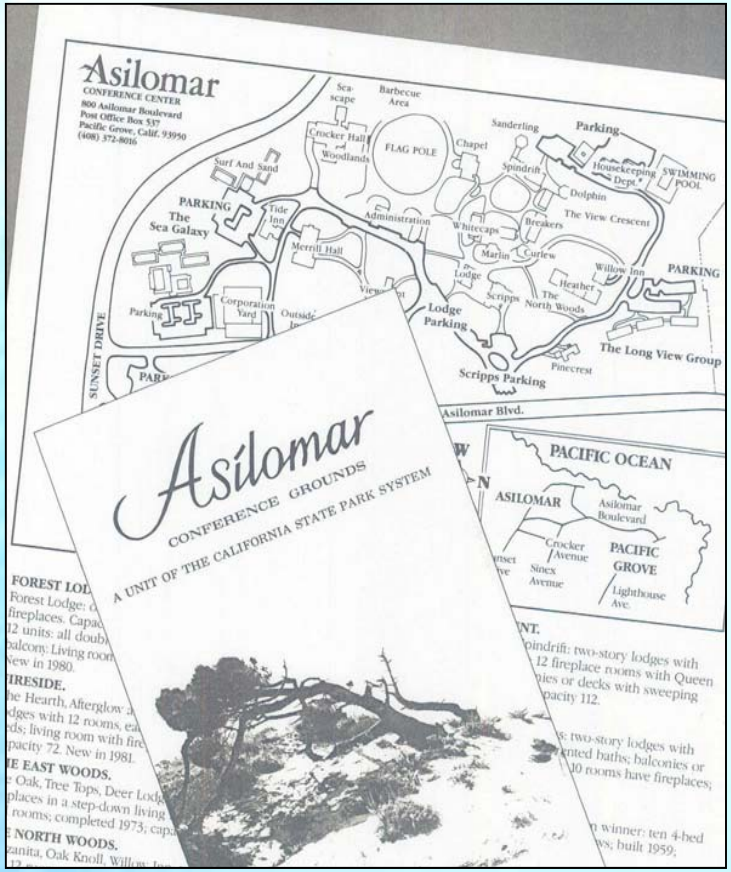
- **NAS Committee Report (July 1974); called for**
  - **A moratorium on certain experiments**
  - **Development of NIH guidelines for conduct and review of recombinant DNA experiments**
  - **An international conference**

Asilomar Scientific Summit (1975)



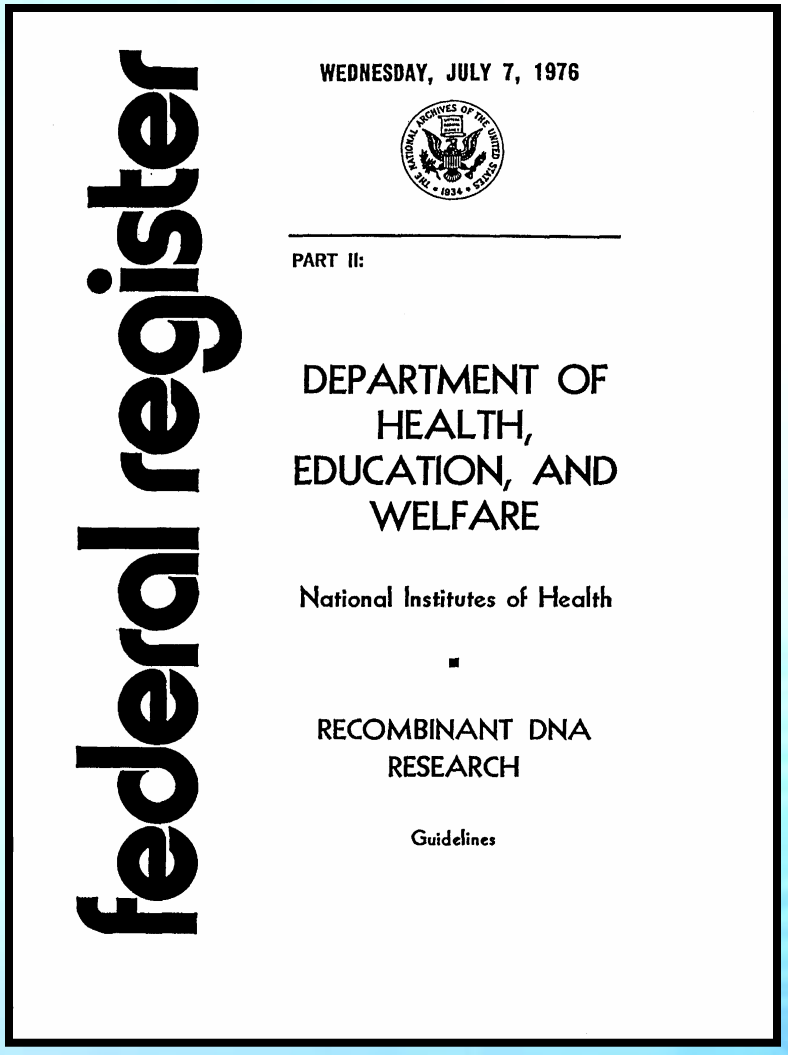
- **Premise:**
  - **Scientists taking responsibility for the risks of their own research activities**
- **Outcomes**
  - **Reaffirmation of the need for guidelines**
  - **Establishment of a new federal oversight committee**

Development of an Oversight System

- **NIH Recombinant DNA Molecule Program Advisory Committee**
  - **Launched process of developing NIH guidelines for recombinant DNA oversight**
  - **Made recommendations about local oversight**
    - **Award NIH grants for recombinant DNA research only after review of risks by an institutional "biohazards" review committee**
      - **Review of physical containment and facilities**
      - **Consideration of local circumstances**

The First *NIH Guidelines*

- **Published in July 1976**
- **Established responsibilities of investigators and institutions**



federal register

WEDNESDAY, JULY 7, 1976

PART II:

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

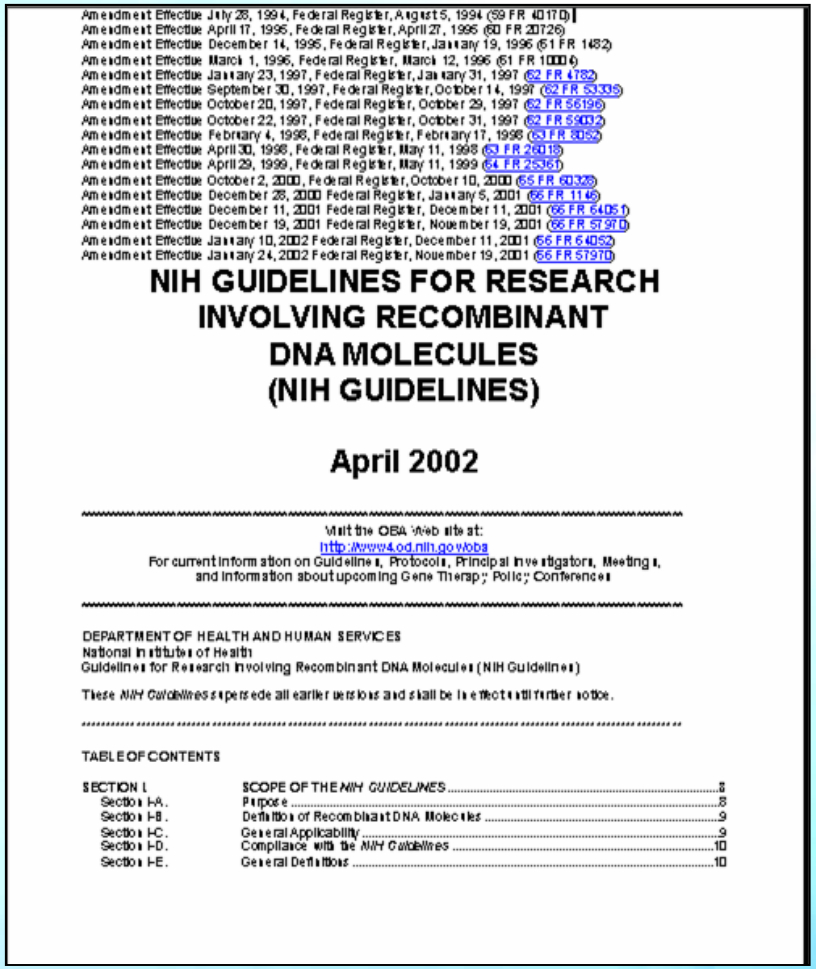
National Institutes of Health

RECOMBINANT DNA RESEARCH

Guidelines

NIH Guidelines for Research Involving Recombinant DNA Molecules

- **A scientifically-responsive document that will continue to evolve**
  - **Have undergone multiple revisions since 1976**
  - **Latest version - April 2002**



Amendment Effective July 28, 1994, Federal Register, August 5, 1994 (59 FR 40170)
Amendment Effective April 17, 1995, Federal Register, April 27, 1995 (60 FR 20726)
Amendment Effective December 14, 1995, Federal Register, January 19, 1996 (61 FR 1482)
Amendment Effective March 1, 1996, Federal Register, March 12, 1996 (61 FR 10004)
Amendment Effective January 23, 1997, Federal Register, January 31, 1997 (62 FR 4782)
Amendment Effective September 30, 1997, Federal Register, October 14, 1997 (62 FR 53335)
Amendment Effective October 20, 1997, Federal Register, October 29, 1997 (62 FR 56196)
Amendment Effective October 22, 1997, Federal Register, October 31, 1997 (62 FR 59032)
Amendment Effective February 4, 1998, Federal Register, February 17, 1998 (63 FR 8052)
Amendment Effective April 30, 1998, Federal Register, May 11, 1998 (63 FR 26018)
Amendment Effective April 29, 1999, Federal Register, May 11, 1999 (64 FR 25361)
Amendment Effective October 2, 2000, Federal Register, October 10, 2000 (65 FR 60328)
Amendment Effective December 28, 2000 Federal Register, January 5, 2001 (66 FR 1146)
Amendment Effective December 11, 2001 Federal Register, December 11, 2001 (66 FR 64051)
Amendment Effective December 19, 2001 Federal Register, November 19, 2001 (66 FR 57970)
Amendment Effective January 10, 2002 Federal Register, December 11, 2001 (66 FR 64052)
Amendment Effective January 24, 2002 Federal Register, November 19, 2001 (66 FR 57970)

NIH GUIDELINES FOR RESEARCH INVOLVING RECOMBINANT DNA MOLECULES (NIH GUIDELINES)

April 2002

Visit the OBA Web site at:
http://www4.od.nih.gov/oba
For current information on Guidelines, Protocols, Principal Investigators, Meetings, and Information about upcoming Gene Therapy Policy Conferences

DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health
Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)

These *NIH Guidelines* supersede all earlier versions and shall be in effect until further notice.

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http://www4.od.nih.gov/oba/rac/guidelines/guidelines.html

Content of the *NIH Guidelines*

- **Section I – Scope**
- **Section II – Safety Considerations**
- **Section III – Types of Experiments Covered**
- **Section IV – Roles and Responsibilities**
- **Appendices**

NIH Guidelines – Section I

- **Scope and Applicability**
  - **Specifies practices for constructing and handling**
    - **Recombinant DNA molecules**
    - **Organisms and viruses containing recombinant DNA molecules**
  - **Definition**
    - **Constructed outside living cells by joining natural or synthetic DNA segments to DNA molecules that can replicate in a living cell**
    - **Molecules resulting from the replication of those described above**
  - **Applicability broader than many NIH grant requirements**

The *NIH Guidelines* Apply to…

- **Recombinant DNA research that is**
  - **Performed at or sponsored by an institution that receives any NIH funding for recombinant DNA research**
- **Rationale: For biosafety to be meaningful, it has to be observed by all investigators at an institution**

Are the *NIH Guidelines* Optional?

- **“Guidelines” does not mean “optional”**
- **They are a term and condition of NIH funding for recombinant DNA research**

Are the *NIH Guidelines* optional?

- **What are potential consequences of noncompliance with the *NIH Guidelines*?**
  - **Suspension, limitation, or termination of NIH funds for recombinant DNA research at the institution, or**
  - **A requirement for prior NIH approval of any or all recombinant DNA projects at the institution.**

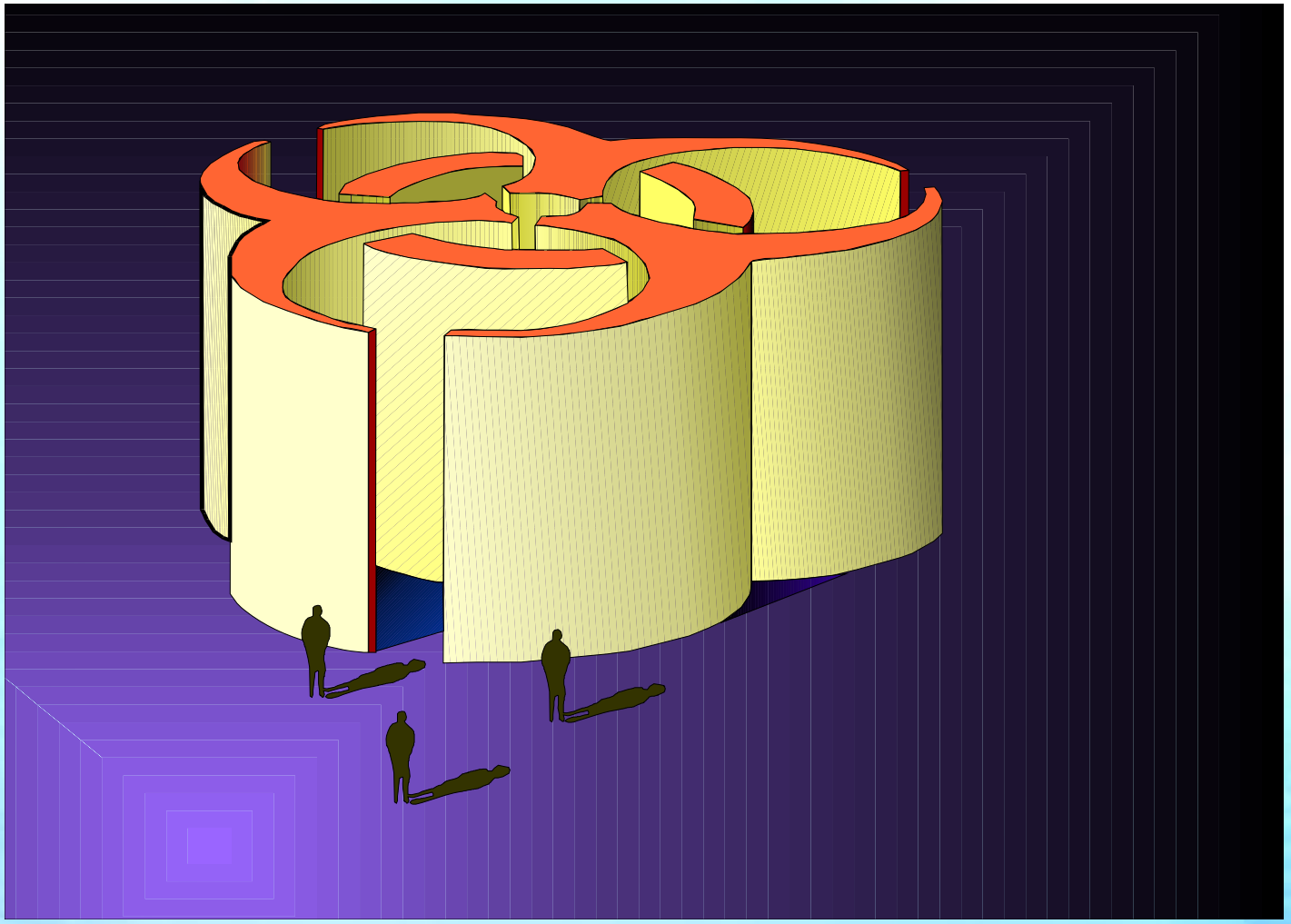
Prescription versus Flexibility

- **Some matters are left to institutional discretion**
- **Flexibility is a two-sided coin**
  - **Accommodates institutional diversity and heterogeneity**
  - **Can create uncertainty about expectations**

Specifics vs. Intent

- **"The *NIH Guidelines* will never be complete or final since all conceivable experiments involving recombinant DNA cannot be foreseen. Therefore, it is the responsibility of the institution and those associated with it to adhere to the intent of the *NIH Guidelines* as well as to the specifics."**
  - **Good judgment is key**
  - **OBA can help**

NIH Guidelines – Section II



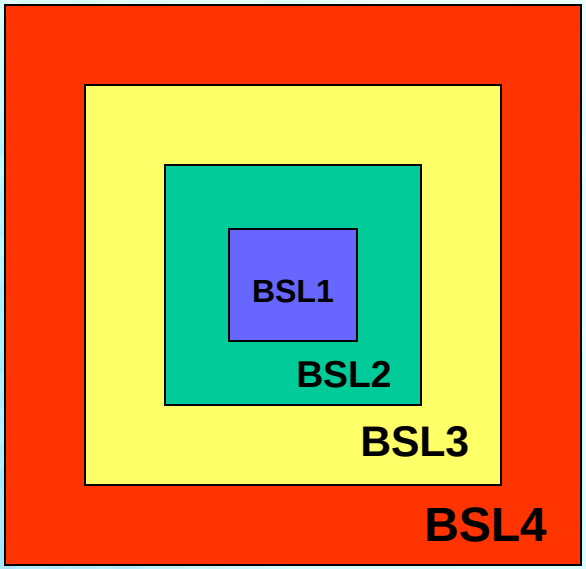
NIH Guidelines – Section II

- **Safety Considerations**
  - **Risk assessments: (Appendix B)**

RG 1	RG 2	RG 3	RG 4
Agents that are not associated with disease in healthy adult humans	Agents that are associated with human disease which is rarely serious and for which preventive or therapeutic interventions are *often* available	Agents that are associated with serious or lethal human disease for which preventive or therapeutic interventions *may be* available (high individual risk but low community risk)	Agents that are likely to cause serious or lethal human disease for which preventive or therapeutic interventions are *not usually* available (high individual risk and high community risk)

NIH Guidelines – Section II

- **Safety Considerations**
  - **Containment**
    - **Physical (Appendix G)**
      - **Practices**
      - **Equipment/facilities**
    - **Biological (Appendix I)**
      - **Survival**
      - **Transmission**



NIH Guidelines – Section III

IBC, RAC, NIH Director

IBC, OBA (in consult with experts)

IBC, IRB, RAC

IBC

IBC (notification)

Exempt

NIH Guidelines - Section III Levels of Review

Level of review	Example of recombinant DNA research	Relevant section(s) of the *NIH Guidelines*
IBC, RAC review, and NIH Director review and approval - Major Action	Experiments that compromise the control of disease agents in medicine through deliberate transfer of a drug resistance trait	III-A
IBC approval and NIH review for containment determinations	Experiments conducted with a recombinant DNA modified restricted agent in a whole animal	III-B
IBC and IRB approval and NIH review before research participant enrollment	Experiments involving the deliberate transfer of recombinant DNA into a human research participant	III-C
IBC approval before initiation	Creating stable germline alterations of an animal's genome, or testing viable recombinant DNA modified microorganisms on whole animals, where BL-2 containment or greater is necessary	III-D
IBC notice at initiation	Creating stable germline alterations of rodents using recombinant DNA when these experiments require only BL-1 containment	III-E
Exempt from the *NIH Guidelines*. IBC registration not required if experiment not covered by Sections III-A, III-B, or III-C	Purchase or transfer of transgenic rodents	III-F

NIH Guidelines – Section IV

- **Roles and Responsibilities**
  - **Institution**
  - **Institutional Biosafety Committee (IBC)**
  - **Biological Safety Officer (BSO)**
  - **Principal Investigator (PI)**
  - **NIH**

Institutional Responsibilities under the *NIH Guidelines*

- **The Institution shall:**
  - **Establish and implement policies for the safe conduct of recombinant DNA research**
  - **Establish an Institutional Biosafety Committee**
  - **Assist and ensure compliance with the *NIH Guidelines* by investigators**
  - **Ensure appropriate training for IBC members and staff, PIs, laboratory staff**
  - **Determine necessity for health surveillance of personnel**
  - **Report any significant problems or violations to OBA within 30 days**

PI Responsibilities under the *NIH Guidelines*

- **The Principal Investigator shall (among other things):**
  - **Initiate or modify no recombinant DNA research which requires IBC approval until approval is granted**
  - **Determine whether experiments are covered under III-E and notify the IBC as appropriate**
  - **Be adequately trained in good microbiological techniques**
  - **Adhere to IBC emergency plans for spills and personnel contamination**
  - **Report any significant problems or violations to OBA within 30 days**

NIH Responsibilities under the *NIH Guidelines*

- **NIH OBA (*on behalf of the NIH Director*)**
  - **Managing the RAC**
  - **Conducting and supporting training of IBCs, BSOs, investigators, laboratory staff**
  - **Convening Scientific Symposia and Gene Therapy Policy Conferences**
  - **Review of:**
    - **Human gene transfer protocols**
    - **Certain basic recombinant DNA experiments**
  - **"Minor actions"**
    - **Changes not requiring approval by the NIH Director**

NIH Responsibilities under the *NIH Guidelines*

- **Basic recombinant DNA experiments reviewed by NIH OBA**
  - **Deliberate transfer of drug resistance trait to microorganisms not known to acquire the trait naturally, if it could compromise disease control**
  - **Cloning of toxin molecules with LD_{50} <100 ng/Kg bodyweight**
  - **DNA from restricted agents transferred to nonpathogenic prokaryotes or lower eukaryotes**
  - **DNA from nonpathogenic prokaryotes or lower eukaryotes transferred to restricted agents**
  - **Use of infectious or defective restricted poxviruses in presence of helper virus**

NIH Guidelines - Appendices

- Appendix A – Exemptions: Natural Exchangers
- Appendix B – Classification of Etiologic Agents
- Appendix C – Exemptions under III-F
- Appendix D – Major Actions
- Appendix E – Certified Host-Vector Systems
- Appendix F – Biosynthesis of Toxic Molecules
- Appendix G – Physical Containment
- Appendix H – Shipment
- Appendix I – Biological Containment

NIH Guidelines - Appendices

- **Appendix J – Biotechnology Research Subcommittee**
- **Appendix K – Large Scale Physical Containment**
- **Appendix L – Gene Therapy Policy Conferences**
- **Appendix M – Points to Consider in Human Gene Transfer Research**
- **Appendix P – Physical and Biological Containment: Plants**
- **Appendix Q – Physical and Biological Containment: Animals**

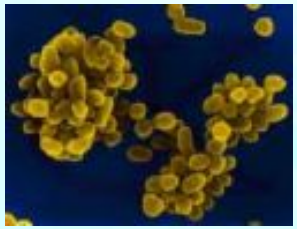
Key Portions of the *NIH Guidelines* Appendix B

Appendix B

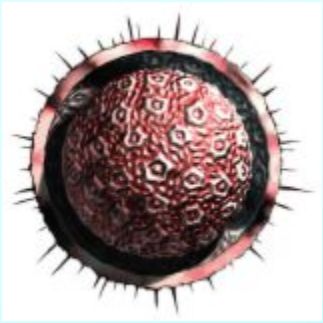
- **Classification of human etiologic agents on the basis of hazard**
  - **Bacterial**
  - **Fungal**
  - **Virus**
  - **Prion**
  - **Parasites**

Fasciola hepatica **RG2**

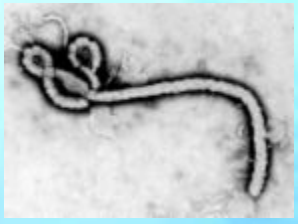
Microsporum **RG2**



Brucella abortus **RG3**



Epstein Barr RG2



Ebola virus RG4

Key Portions of the *NIH Guidelines* Appendix G

Appendix G

- Specifies details of containment and confinement for standard <u>laboratory</u> practices
- Defines Biosafety Level 1 through Biosafety Level 4
- Appropriate for animals that are worked with in a laboratory setting

Key Portions of the *NIH Guidelines* Appendix I

Appendix I

- **Biological containment barriers**
  - **Limit the infectivity of a vector or vehicle (plasmid or virus) for specific hosts**
  - **Limit dissemination and survival of a vector in the environment**
- **Vectors can be genetically designed to decrease, by many orders of magnitude, the probability of dissemination of recombinant DNA outside the laboratory**

Key Portions of the *NIH Guidelines* Appendix M

Appendix M

- **Points to Consider in the design and submission of protocols for the transfer of recombinant DNA Molecules into one or more human research participants.**
  - **Requirements for Protocol Submission, Review, and Reporting**

Key Portions of the *NIH Guidelines* Appendix Q

Appendix Q

- **Applies when research animals are of a size or have growth requirements that preclude laboratory containment**
  - **For example, cattle, swine, sheep, goats, horses, poultry, etc.**
- **Addresses containment and confinement practices in <u>animal facilities</u> (BL1-N to BL4-N)**

Need more information?

- **NIH OBA provides oversight, guidance, and resources**
  - **Staff and information resources available to help ensure investigators and their institutions are compliant with the *NIH Guidelines***
  - **Scientific and medical staff available to answer queries**
    - **Interpretation of *NIH Guidelines***
    - **Containment**
    - **Exemptions**
    - **Risk group classification**

Need more information?

- Institutional Biosafety Officer
- Institutional Biosafety Committee
  - Lab Safety Issues
    - Personal protective equipment for personnel
    - Disposal of waste
    - Decontamination of laboratory and equipment
    - Containment facilities
    - Accidents (emergency plans and response)

Questions?