

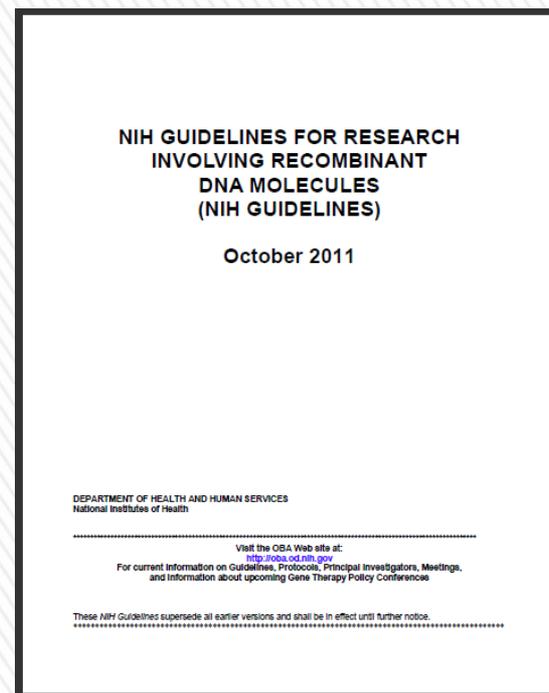
A large, 3D rendering of a DNA double helix is positioned on the left side of the slide. It is shown in a light blue/white color and is oriented vertically, winding upwards. The background behind the helix is a gradient of light blue.

# **Overview of the *NIH Guidelines* for *Research Involving* *Recombinant DNA Molecules***



# ***NIH Guidelines***

- **A scientifically responsive document that will continue to evolve**
  - **Has undergone multiple revisions since 1976**
  - **Latest version – October, 2011**



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





# Amended *NIH Guidelines*



- ***NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules***
- **Final Action notice published September 5, 2012**
- **Requirements go into effect March 5, 2013**





# **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:**
  - 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:**
  - 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**





# Aren't they just *Guidelines*?

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





# Are the *NIH Guidelines* Optional?

- **There 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 research projects at the institution**





# Are the *NIH Guidelines* Optional?

- **There 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 research projects at the institution**





# Prescription vs. 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 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**



# Section II - Safety Considerations





# Section II - Safety Considerations

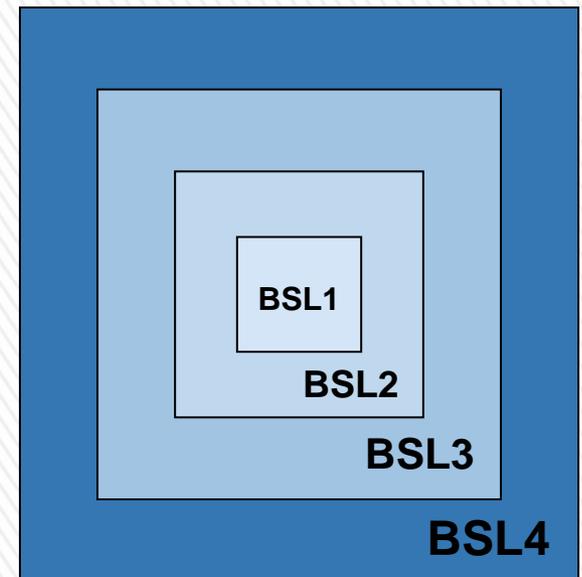
- Risk Groups (Appendix B)

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



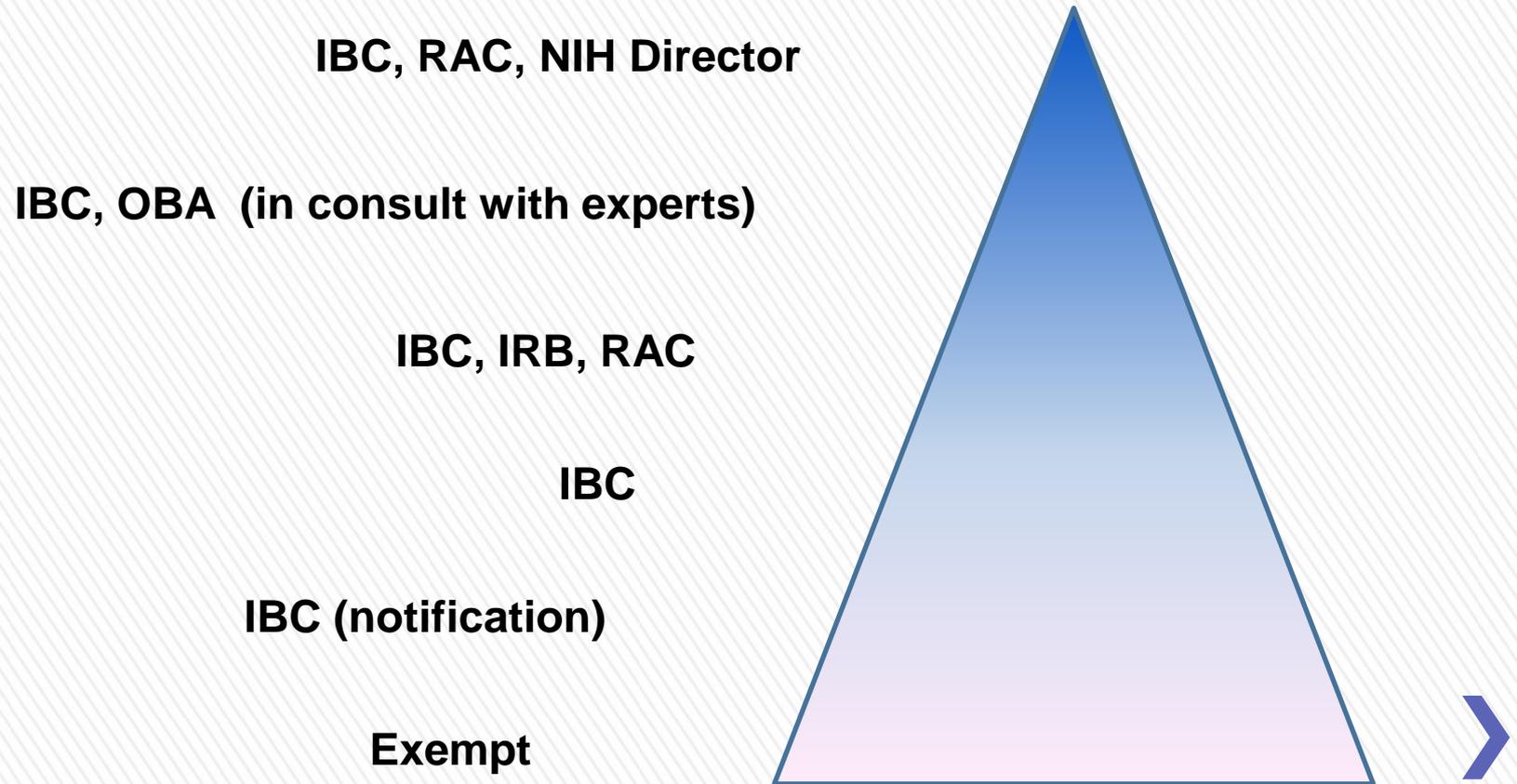
# Section II - Safety Considerations

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





# Section III - Levels of Review





# Section III - Levels of Review

| Level of review  | Example of recombinant DNA research  | Relevant section(s) of the <i>NIH Guidelines</i> |
|--|--|--|
| IBC, RAC review, and NIH Director review and approval  | Experiments that compromise the control of disease agents in medicine through deliberate transfer of a drug resistance trait   | <b>III-A</b>                                     |
| IBC approval and NIH review for containment determinations   | Experiment involving the cloning of toxin molecules with LD50 of less than 100 nanograms per kilogram of body weight   | <b>III-B</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   | <b>III-C</b>                                     |
| 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 | <b>III-D</b>                                     |
| IBC notice at initiation   | Creating stable germline alterations of rodents using recombinant DNA when these experiments require only BL-1 containment   | <b>III-E</b>                                     |
| Exempt from the <i>NIH Guidelines</i> . IBC registration not required if experiment not covered by Sections III-A, III-B, or III-C | Purchase or transfer of transgenic rodents   | <b>III-F</b>                                     |



# ***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 accidents, incidents or violations to OBA within 30 days (or immediately as required)**





# ***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**

**\* Use current DOT/IATA regulations**





# ***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**





**Requirements for  
Institutional Biosafety  
Committees (IBCs) in  
the *NIH Guidelines***



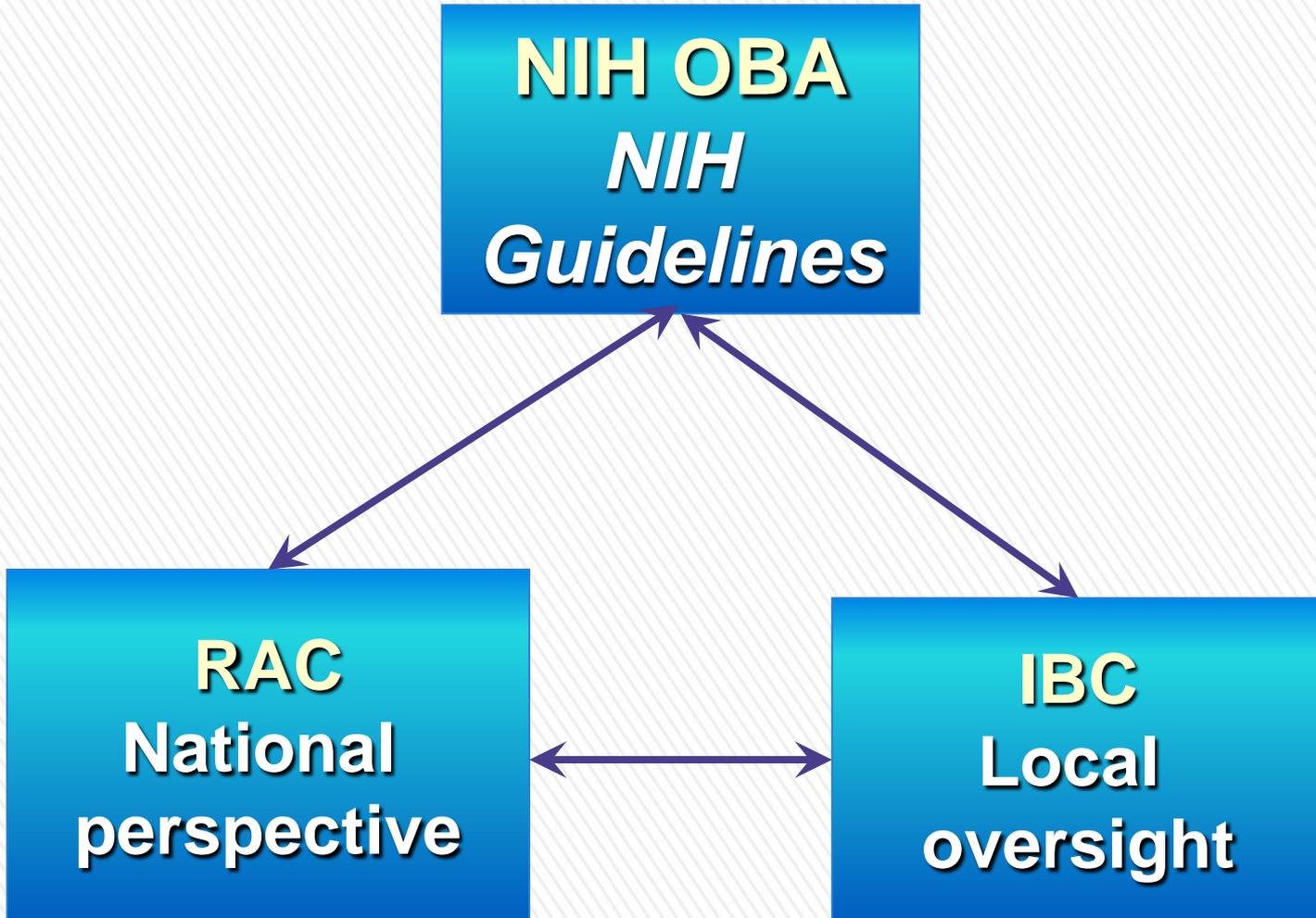
# IBCs

***The cornerstone of oversight of recombinant DNA research at the local level***





# IBCs and NIH - Partners in the Oversight of Recombinant DNA Research





# IBCs

- Established under the *NIH Guidelines* specifically for the review of recombinant (and synthetic) nucleic acid research





# IBCs

- **IBCs are increasingly assigned additional responsibilities**
  - **Select Agent research**
  - **Research entailing risk of exposure to blood borne pathogens**
  - **Stem cell research**
  - **Nanotechnology**
  - **“Dual Use” research**
  
- **Broader purview is a matter of institutional discretion**





# Assembling an IBC

- **Membership:**
  - **No fewer than 5 individuals**
  - **Appropriate scientific and biosafety expertise collectively**
  - **Plant and animal experts, biosafety officer as appropriate**
  - **At least two members not affiliated with the institution**





# Assembling an IBC

- **Expertise:**

- **Expertise in assessment of biological risks to environment and public health**
- **Knowledge of institutional commitments and policies, applicable law, professional standards, community attitudes, and environment**
- **Biological safety and physical containment**
- **Laboratory technical staff (recommended)**





# Assembling an IBC

- **Biological Safety Officer**
  - **BSO must be appointed and made a member of the IBC if research is:**
    - **Large scale (>10 L)**
    - **BL-3 or BL-4**





# **Assembling an IBC**

- **The BSO's duties include:**
  - ❑ **Periodic inspection of labs**
  - ❑ **Reporting to the IBC and institution of any problems, violations, research-related accidents or illnesses**
  - ❑ **Developing emergency plans for handling accidental spills and personnel contamination**
  - ❑ **Advice on lab security**
  - ❑ **Technical advice to PIs and IBCs on research safety procedures**





# Assembling an IBC

- **Non-institutional members - Who are they?**
  - **Representatives of community interests with respect to health and protection of the environment**
  - **E.g., officials of state or local public health or environmental authorities, local government bodies, persons with medical, occupational, or environmental expertise**
  - **They should be the individuals who “represent community attitudes”**





# Staffing the IBC

- **Not prescribed in the *NIH Guidelines***
  - ❑ **IBC Administrator**
  - ❑ **Biological Safety Officer**
  - ❑ **Compliance Officer**
  - ❑ **Manager of Environmental Health and Safety**
  - ❑ **Others**





# ***Ad hoc* Consultants**

- **Use when reviewing research outside the expertise of your members.**





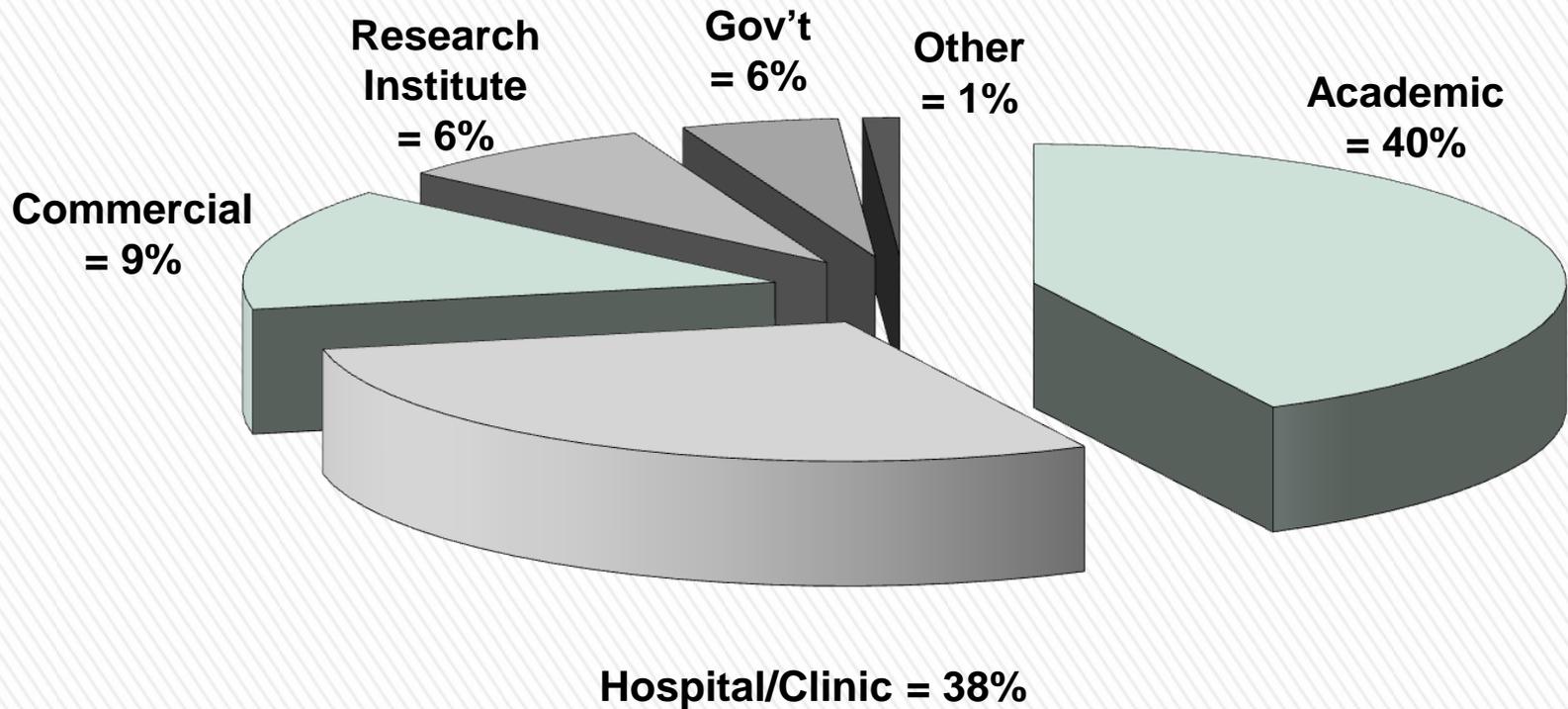
# Registering an IBC

- **Register the IBC with OBA and file annual membership updates**
  - **A roster of IBC members**
    - **Clearly indicate chair, contact person, and special expertise as appropriate (BSO, animal, plant, human gene transfer)**
  - **Biographical sketches of all members**





# IBCs Registered with NIH OBA



September 2012 = 860





# IBC Responsibilities

- In a nutshell, what must IBCs review?
  - Recombinant DNA research for conformity with the *NIH Guidelines*
  - Potential risk to environment and public health
    - Containment levels per *NIH Guidelines*
    - Adequacy of facilities, SOPs, PI and lab personnel training
    - Institutional and investigator compliance; e.g., adverse event reports





# IBC Responsibilities

- **In basic and preclinical research, IBCs have authority to:**
  - **Lower containment levels for certain experiments in which DNA from Risk Group 2-4 is cloned in non-pathogenic organisms**
  - **Set containment levels for experiments involving whole plants and animals**
  - **Review periodically institutional compliance with *NIH Guidelines***
  - **Adopt emergency plans covering spills, contamination, other accidents**





# IBC Responsibilities

- **In human gene transfer research, IBCs must also ensure:**
  - ❑ **No participant enrolled until RAC review, IBC and IRB approval obtained**
  - ❑ **Issues raised by RAC in public review are considered**
  - ❑ **Final IBC approval occurs only after RAC review**
  - ❑ **Compliance with surveillance, data reporting, and adverse event reporting**





# IBCs and NIH OBA

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





# OBA Outreach and Education

- **Policy and professional development conferences for IBCs**
- **Training courses and presentations at key professional and scientific meetings**
- **IBC resources on OBA's web site**
  - *NIH Guidelines and Federal Register* notices
  - Reports of safety symposia
  - “Latest news” items on meetings, policy guidance, resources, compliance notices, etc.
  - FAQs
  - Training materials: Slide Presentations and Video of Professional Development Workshops





# Tools You Can Use





# Tools You Can Use



## Transgenic Animals and the Use of Recombinant DNA in Animals FAQs for Research Subject to the NIH Guidelines



### Under which section of the NIH Guidelines does the generation of transgenic rodents fall?

The creation of transgenic rodents falls under one of two portions of the *NIH Guidelines* depending on the containment level required to house the rodents. Experiments involving the creation of transgenic rodents that can be housed under Biosafety Level 1 conditions are covered under **Section III-E-3**. Experiments involving the generation of transgenic rodents requiring BL2, BL3 and BL4 containment are covered under **Section III-D-4**.

### Under which section of the NIH Guidelines does the generation of transgenic animals other than rodents fall?

The creation of all transgenic animals (other than rodents that can be housed under BL1 containment conditions) is covered under **Section III-D-4** of the *NIH Guidelines*.

### Would the breeding of two different strains of knock-out mice require IBC approval under the NIH Guidelines?

The techniques used initially to create knock-out animals involve the stable introduction of recombinant DNA into the animal's genome, and thus these animals are considered transgenic. As the breeding of two different strains of knock-out mice will potentially generate a novel strain of transgenic animal, the work may be covered under the *NIH Guidelines* and require IBC review and approval. Sections in the *NIH Guidelines* that cover work with rodents include **III-E-3** for work that requires Biosafety Level (BL) 1 containment and **III-D-4** for work that requires BL2, BL3 and BL4 containment. Certain breeding experiments are exempt under Appendix C-VII the *NIH Guidelines*. This exemption covers the breeding of two different transgenic rodents or the breeding of a transgenic rodent and a non-transgenic rodent with the intent of creating a new strain of transgenic rodent that can be housed at BL1 if:

- (1) Both parental rodents can be housed under BL1 containment; and
- (2) neither parental transgenic rodent contains the following genetic modifications: (i) incorporation of more than one-half of the genome of an exogenous eukaryotic virus from a single family of viruses; or (ii) incorporation of a transgene that is under the control of a gammaretroviral long terminal repeat (LTR); and (3) the transgenic rodent that results from this breeding is not expected to contain more than one-half of an exogenous viral genome from a single family of viruses.

### Is IBC registration and approval needed for the maintenance of a transgenic animal colony?

The maintenance of a transgenic rodent colony (i.e. breeding within a particular transgenic strain) at BL1 is an activity that is exempt from the *NIH Guidelines* and, as such, does not require IBC registration and approval. The maintenance of a transgenic rodent colony at BL2 or higher falls under **Section III-D-4-b** and requires IBC approval. The breeding of all other transgenic animals is subject to the *NIH Guidelines* under **Section III-D-4-a** or **III-D-4-b** depending on the containment level required.

### Is the purchase and transfer of transgenic rodents exempt from the NIH Guidelines?

Under **Appendix C-VI** of the *NIH Guidelines*, the purchase or transfer of transgenic rodents may be maintained at BL1 containment are exempt from the *NIH Guidelines*. The purchase or transfer of transgenic rodents that require BL2 or higher containment is **not** exempt from the *NIH Guidelines*. These animals are covered under **Section III-D-4**, and purchase and transfer of such animals requires IBC registration and approval.



## Animal experiments covered under the NIH Guidelines for Research Involving Recombinant DNA Molecules



| ACTIVITY   | MINIMUM BSL         | SECTION                 |
|--|---------------------|-------------------------|
| <b>CREATION OF TRANSGENIC ANIMALS</b>  |                     |                         |
| Creation of transgenic rodents   | BL1                 | III-E-3                 |
| Creation of transgenic rodents   | BL2 or higher       | III-D-4-b               |
| Creation of transgenic animals other than rodents  | BL1/BL1-N           | III-D-4-a               |
| Creation of transgenic animals other than rodents  | BL2/BL2-N or higher | III-D-4-b               |
| Creation of recombinant DNA modified arthropods  | BL1                 | III-D-4-a               |
| Creation of recombinant DNA modified arthropods  | BL2 or higher       | III-D-4-b               |
| Creation of knock-out rodents  | BL1                 | III-E-3                 |
| Creation of knock-out rodents  | BL2 or higher       | III-D-4-b               |
| <b>BREEDING OF TRANSGENIC ANIMALS</b>  |                     |                         |
| Breeding rodents from one strain (propagation/colony maintenance)  | BL1                 | Exempt (III-F-4)        |
| Breeding rodents from one strain (propagation/colony maintenance)  | BL2 or higher       | III-D-4-b               |
| Breeding rodents from two strains (generating a new strain) providing neither parental rodent contains the following genetic modifications: (i) incorporation of more than one-half of the genome of an exogenous eukaryotic virus from a single family of viruses; or (ii) incorporation of a transgene that is under the control of a gammaretroviral long terminal repeat (LTR); and (3) the rodent that results from the breeding is not expected to contain more than one-half of an exogenous viral genome from a single family of viruses.    | BL1                 | Exempt (Appendix C-VII) |
| Breeding rodents from two strains (generating new strain) if the parental rodent contains the following genetic modifications: (i) incorporation of more than one-half of the genome of an exogenous eukaryotic virus from a single family of viruses; or (ii) incorporation of a transgene that is under the control of a gammaretroviral long terminal repeat (LTR); and (3) the rodent that results from the breeding contains more than one-half of an exogenous viral genome from a single family of viruses.                                   | BL1                 | III-E-3                 |
| Breeding rodents from two strains (generating new strain)  | BL2 or higher       | III-D-4-b               |
| Breeding of transgenic animals other than rodents  | BL1                 | III-D-4                 |
| Breeding of transgenic animals other than rodents  | BL2 or higher       | III-D-4                 |
| Breeding of recombinant DNA modified arthropods  | BL1                 | Exempt (III-F-4)        |
| Breeding of recombinant DNA modified arthropods  | BL2 or higher       | III-D-4-b               |
| Breeding of knockouts (propagation)  | BL1                 | Exempt (III-F-4)        |
| Breeding of knockouts (propagation)  | BL2 or higher       | III-D-4-b               |
| Breeding of knockouts from two strains (generating new strain) providing neither parental rodent contains the following genetic modifications: (i) incorporation of more than one-half of the genome of an exogenous eukaryotic virus from a single family of viruses; or (ii) incorporation of a transgene that is under the control of a gammaretroviral long terminal repeat (LTR); and (3) the rodent that results from the breeding is not expected to contain more than one-half of an exogenous viral genome from a single family of viruses. | BL1                 | Exempt (Appendix C-VII) |





# Tools You Can Use

National Institutes of Health • Office of Biotechnology Activities



## Information for Labs Conducting Recombinant DNA Research

### Reporting of Incidents Involving Recombinant DNA to the NIH Office of Biotechnology Activities (OBA)

#### • What kinds of incidents involving recombinant DNA must be reported to the NIH OBA?

The *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* states that "...any significant problems, violations of the *NIH Guidelines*, or any significant research-related accidents and illnesses" must be reported to NIH OBA within 30 days. Certain types of accidents must be reported on a more expedited basis. Spills or accidents in BL2 laboratories resulting in an overt exposure must be immediately reported to NIH OBA. Spills or accidents occurring in high containment (BL3 or BL4) laboratories resulting in an overt or potential exposure must be immediately reported to NIH OBA.

#### • How serious must a problem be to warrant reporting to OBA?

Any spill or accident involving recombinant DNA research of the nature described above or that otherwise leads to personal injury or illness or to a breach of containment must be reported to OBA. These kinds of events might include skin punctures with needles containing recombinant DNA, the escape or improper disposition of a transgenic animal, or spills of high-risk recombinant materials occurring outside of a biosafety cabinet. Failure to adhere to the containment and biosafety practices articulated in the *NIH Guidelines* must also be reported to OBA.

Minor spills of low-risk agents not involving a breach of containment that were properly cleaned and decontaminated generally do not need to be reported. OBA should be consulted if the Institutional Biosafety Committee (IBC), investigator, or other institutional staff are uncertain whether the nature or severity of the incident warrants reporting; OBA can assist in making this determination.

#### • Who is responsible for reporting incidents involving recombinant DNA to NIH OBA?

Under the *NIH Guidelines* incident reporting is articulated as a responsibility of the Institution, IBC, Biological Safety Officer, and Principal Investigator. Institutions have the discretion to determine which party should make these reports, and one report for each incident or set of information is generally sufficient.

### Template for Reporting Incidents Involving Recombinant DNA to the NIH Office of Biotechnology Activities (OBA)

The *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)* states that "...any significant problems, violations of the *NIH Guidelines*, or any significant research-related accidents and illnesses" must be reported to NIH OBA within 30 days. Certain types of incidents must be reported on a more expedited basis. Spills or accidents in BL2 laboratories resulting in an overt exposure must be immediately reported to NIH OBA. Spills or accidents occurring in high containment (BL3 or BL4) laboratories resulting in an overt or potential exposure must be immediately reported to NIH OBA.

This template is intended to facilitate the reporting of incidents that occur during the conduct of research subject to the *NIH Guidelines*. You may download this template as a Word document and the fields will expand according to the amount of text entered. Use of this template is not required and other formats may be acceptable.

A separate template for reporting Human Gene Transfer Adverse Events is available at:  
[http://www4.od.nih.gov/oba/RAC/Adverse\\_Event\\_Template.doc](http://www4.od.nih.gov/oba/RAC/Adverse_Event_Template.doc)

Please note that submitting this completed template to NIH OBA does NOT fulfill the reporting requirements of other agencies. You should verify with the other parties to whom you must report whether the use of this template is acceptable.

Completed reports may be sent via U.S. mail, courier service, e-mail, or facsimile to:

Attention: Incident Reports  
NIH Office of Biotechnology Activities  
6705 Rockledge Drive, Suite 750  
Bethesda, Maryland 20892-7985  
(For all non-USPS deliveries use Zip Code 20817)  
Telephone 301-496-9838  
Fax 301-496-9839  
E-mail: [oba@od.nih.gov](mailto:oba@od.nih.gov)

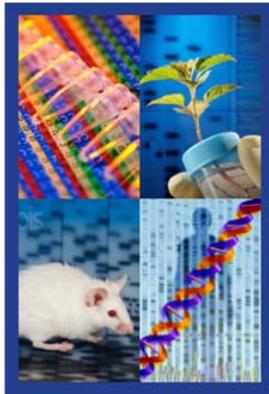




# Tools You Can Use

National Institutes of Health  
Office of Biotechnology Activities

## Investigator Responsibilities



under the  
**NIH Guidelines  
for Research Involving  
Recombinant DNA  
Molecules**



NIH Office of Biotechnology Activities



## Does your research involve recombinant DNA?

Then you should know about the:

### NIH Office of Biotechnology Activities

OBA promotes science, safety and ethics in biotechnology through advancement of knowledge, enhancement of public understanding, and development of sound public policies. A core responsibility of OBA is to ensure that research involving recombinant DNA is conducted in keeping with the *NIH Guidelines for Research Involving Recombinant DNA Molecules*.

### NIH Guidelines for Research Involving Recombinant DNA Molecules

The *NIH Guidelines* detail procedures and practices for the containment and safe conduct of various forms of recombinant DNA research, including research involving genetically modified plants and animals, and human gene transfer. A requirement of the *NIH Guidelines* is that an Institutional Biosafety Committee must review and approve all research subject to the *NIH Guidelines*.

### Institutional Biosafety Committee

Institutional Biosafety Committees (IBCs) provide local review and oversight of nearly all forms of research utilizing recombinant DNA. They ensure that recombinant DNA research conducted at or sponsored by the institution is in compliance with the *NIH Guidelines*.

## Have your projects been registered with the IBC?

IBC CONTACT \_\_\_\_\_

Visit OBA on the web: <http://www4.od.nih.gov/oba> or write to [oba@od.nih.gov](mailto:oba@od.nih.gov)





# **OBA News**

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- **In body of message:**

**Subscribe OBA\_NEWS**





# OBA Contact Information



National Institutes of Health

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# Questions?

