

**Major Actions under Section III-A of the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines)***

**1. What experiments are considered to be Major Actions under the *NIH Guidelines*?**

The deliberate transfer of a drug resistance trait to a microorganism, when such a transfer could compromise the use of the drug to control disease agents in humans, veterinary medicine, or agriculture, is a Major Action (see Section III-A-1-a of the *NIH Guidelines*).

**2. What criteria should be used to determine if the transfer of a particular drug resistance trait is considered a Major Action under Section III-A-1-a of the *NIH Guidelines*?**

An experiment is considered to be a Major Action if it involves the acquisition of resistance to a drug that is considered to be a first-line or second-line treatment against a given disease causing microorganism. This includes whether the drug is important for the treatment of a specific patient population (for example, children or immunocompromised individuals), as well as the use of the drug as a treatment outside of the United States (for example, Chloramphenicol is not in widespread use in the U.S. but is a commonly used antibiotic in many other countries).

**3. What are the review requirements for Major Actions?**

Experiments considered Major Actions under the *NIH Guidelines* cannot be initiated without submission of relevant information on the proposed experiment to the NIH Office of Biotechnology Activities, the publication of the proposal in the *Federal Register* for 15 days of comment, and review by the NIH Recombinant DNA Advisory Committee (RAC). The RAC reviews the proposed research and makes recommendations to the NIH Director regarding whether the work may be conducted and, if so, what the containment conditions or special requirements for such experiments should be.

**4. Who approves Major Actions?**

The NIH Director approves Major Action experiments. These experiments may not proceed unless approved by the NIH Director. These experiments also require Institutional Biosafety Committee (IBC) review and approval before initiation.

**5. Once a Major Action has been approved can anyone perform such experiments?**

Unless otherwise specified by the NIH Director, approval to conduct a Major Action experiment is granted only to the investigators who submitted the proposal. If other investigators, even those at the same institution, wish to conduct similar work they must also seek approval from NIH.

**6. Does the IBC need to review a Major Action proposal before it is sent to OBA?**

The IBC may review these experiments before or after review by the RAC. However, it should be noted that the work cannot be initiated unless approval is granted by the NIH Director. Furthermore, the IBC should take into consideration any special conditions that the NIH Director has stipulated and ensure they are observed.

**7. Transfer of certain antibiotic resistance into an organism on the HHS/USDA Select Agent lists requires approval from those agencies. Do I also need to submit a request to OBA for approval?**

All experiments utilizing recombinant DNA that involve the deliberate transfer of a drug resistance trait into a Select Agent (restricted experiments) are subject to the regulatory authority of, and review by, HHS or USDA under their respective rules in either 42 CFR Part 73, 7 CFR Part 331, and 9 CFR Part 121. Review and approval by the appropriate federal agency according to these rules eliminates the requirement for NIH review and approval under the *NIH Guidelines*. However, the other provisions of the *NIH Guidelines* - for example, IBC review and approval - are still applicable.

**8. What information needs to be submitted to OBA for review of a Major Action experiment?**

The following elements comprise a baseline or core set of information that can inform OBA and RAC deliberations of Major Actions under Section III-A-1-a of the *NIH Guidelines*. Not all informational elements will be necessary in every case, and in some cases additional information may be deemed necessary.

- Information about the proposed experiment
  - Protocol, including technical information about the proposed transfer of antibiotic resistance (e.g., the vector, gene encoding the resistance, level of resistance, cross-reactivity to the antibiotics etc)
  - Rationale for why the work should go forward in light of potential implications for public health, including any scientific and public health benefits of the work that could be accomplished with the construct in hand
  - Availability of alternative approaches to doing the work without conferring resistance to a drug with clinical utility and whether submitting investigator or others have pursued the alternatives
  
- Information specific to the proposed experiment that qualifies as a Major Action under the *NIH Guidelines*
  - Description of the biosafety features of the room(s) in which the work will be conducted
  - Most recent inspection report(s) of the room(s) in which the work will be conducted; also note any biosafety equipment failures or biosafety-related problems that have occurred in these rooms in the last two years
  - Biosafety manual for the proposed work

- Description of any additional biosafety training staff will receive specific to the work in question
- Description of any occupational health requirements for the workers involved in the work in question
- Minutes of any IBC discussion of the protocol in question (IBC may not have discussed the protocol since it would require prior approval by NIH Director)
- IBC contact information

Submission of relevant information on a proposed Major Action should be made to:

Office of Biotechnology Activities  
National Institutes of Health  
6705 Rockledge Drive, Suite 750  
MSC 7985, Bethesda, MD 20892-7985 (20817 for non-USPS mail)  
Telephone: (301) 496-9838  
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