



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*). Because of the potential implications for public health, animals or agriculture such experiments warrant special review.

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 may be considered a Major Action if it involves 1) the deliberate introduction of resistance to a drug into a microorganism and 2) that drug is used to treat disease caused by this organism, in humans, animals or agriculture. A drug is considered to be useful for treatment even if its use is limited to the treatment of a specific patient population (for example, children or immunocompromised individuals), or it is primarily used for 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 requirements for review of 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, review by the NIH Recombinant DNA Advisory Committee (RAC), approval by the NIH Director who stipulates the containment conditions and any special requirements for the experiments.

4. Who approves Major Actions?

The NIH Director approves Major Action experiments after consideration of the RAC's recommendations and any public comments. 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 investigator(s) 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 as a new Major Action.

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 work cannot be initiated unless approval is granted by the NIH Director. If the work is approved

by the NIH Director, the IBC must take into account any special conditions that the NIH Director has stipulated and ensure they are observed when granting institutional approval.

7. Transfer of resistance to certain antibiotics 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 42 CFR Part 73, 7 CFR Part 331, and 9 CFR Part 121. Review and approval by the appropriate federal agency (HHS or USDA) eliminates the requirement for RAC review and NIH Director 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 information is required in order for OBA to determine whether the experiment qualifies as a Major Action under Section III-A-1-a of the *NIH Guidelines*:

- Information about the proposed experiment, including technical information about the proposed transfer of drug resistance (e.g., the vector(s), gene(s) encoding the resistance, degree(s) of resistance, cross-resistance to other drugs etc).

If the experiment is considered to be a Major Action and therefore will be reviewed by the RAC, the following additional information must be submitted to OBA:

- Rationale for why the work should go forward, including an assessment of how the scientific and public health benefits outweigh the potential risks for humans, animals or agriculture.
- A discussion of whether there are alternative approaches to this research that would not involve conferring resistance to a drug that has utility in the treatment of the organism in question. This should include a statement as to whether the submitting investigator or others have pursued any alternatives.
- A description of the proposed risk mitigation strategies that will be implemented to both minimize risk to laboratory personnel as well as the public.
- Minutes, if available, of any IBC discussion of the research in question (IBC review is not required prior to NIH approval, but a preliminary review is desirable).
- IBC contact information.

In addition, OBA may also request the following information be submitted:

- 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, including any reports of 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 that staff will receive specific to the work in question.

- Description of any special occupational health requirements for the workers involved in the work in question (e.g. vaccination).

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
 Fax: (301) 496-9839
 Email: rosenthg@od.nih.gov
 oba@od.nih.gov

Useful Links and Resources

Principles and Practice of Infectious Diseases

(Available on MDConsult.com)

Authors: Gerald L. Mandell, John E. Bennett, and Raphael Dolin

Publisher: Churchill Livingstone

ISBN-13: 978-0443066436

Sanford Guide to Antimicrobial Therapy 2007 (or updated editions)

Authors: David N. Gilbert, Robert C. Moellering and Merle A. Sande

Publisher: Antimicrobial Therapy

ISBN-13: 978-1930808300

Up to Date Online

<http://www.uptodateonline.com/utd/index.do>

Johns Hopkins ABX Guide

<http://www.hopkins-abxguide.org/>

Centers for Disease Control and Prevention

<http://www.cdc.gov/>

Red Book: Report of the Committee on Infectious Diseases

Publisher: American Academy of Pediatrics

ISBN-13: 978-1581101942

Control of Communicable Diseases Manual

Author: David L., Ed. Heymann

Publisher: American Public Health Association

ISBN-13: 978-0875530345

Principles and Practice of Pediatric Infectious Disease

Authors: Sarah S. Long, Larry K. Pickering, and Charles G. Prober

Publisher: Saunders

ISBN-13: 978-0443066870

PubMed: <http://www.ncbi.nlm.nih.gov/sites/entrez>

Medline: <http://www.nlm.nih.gov/medlineplus/>

WHO

<http://www.who.int/en/>

RAC Discussions of Major Actions: <http://www4.od.nih.gov/oba/rac/meeting.html>

June 2007 RAC Meeting: Transfer of tetracycline resistance to *Chlamydia trachomatis*

September 2007 RAC Meeting: Transfer of chloramphenicol resistance to *Rickettsia conorii* and *Rickettsia typhi*

December 2007 RAC Meeting: Transfer of chloramphenicol resistance to *Rickettsia conorii* and *Rickettsia typhi*
 (continued)