

Major Actions under Section III-A of the *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)*

1. What experiments are considered “Major Actions” under the *NIH Guidelines*?

Under the *NIH Guidelines*, the term “Major Action” means that NIH Director approval is required. Only one type of experiment requires NIH Director approval – the deliberate transfer of a drug resistance trait to a microorganism when such resistance could compromise the ability to control the disease agent in humans, veterinary medicine, or agriculture (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 may be considered a Major Action if: 1) it involves the use of recombinant or synthetic nucleic acids to introduce drug resistance into a microorganism, and 2) the drug in question is used to treat disease caused by the organism in humans, veterinary medicine, or agriculture. The experiment would not be considered a Major Action if there is sufficient documentation that resistance to a therapeutically useful concentration of that drug exists in the agent outside of a laboratory setting. Such evidence should be in the form of articles published in the scientific literature.

3. What is considered a therapeutically useful drug?

A drug is therapeutically useful if it is effective in the treatment of the disease caused by the microorganism. It does not have to be the ‘first line’ agent, but should be recognized in the scientific literature as a useful drug. *In vitro* sensitivity to the drug is not sufficient; it must be useful *in vivo*. In addition, if a drug is not therapeutically useful but will confer cross resistance to a therapeutically useful drug then this also is considered a III-A-1-a experiment.

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 pregnant women), or it is primarily used for treatment outside of the United States where alternative drugs are not available (e.g., chloramphenicol is not in common use in the U.S. but is used in many other countries).

4. Can an Institutional Biosafety Committee (IBC) determine if a particular experiment meets the criteria of Section III-A-1-a or must NIH make the determination?

The determination regarding whether a particular experiment constitutes a Major Action initially should be made by the investigator and confirmed by the IBC. IBCs are encouraged to contact the NIH Office of Biotechnology Activities (OBA) if they need assistance in determining whether a specific experiment involving the deliberate transfer of a drug resistance trait falls under Section III-A-1-a and therefore requires NIH Recombinant DNA Advisory Committee (RAC) review and NIH Director approval. IBCs may also consult with OBA regarding experiments that raise important public health issues but do not meet the criteria of Section III-A-1-a (e.g., because there is low frequency of resistance to a drug). OBA will consult, as needed, with experts who may include members of the RAC.

5. What are the steps in the review process for a Section III-A-1-a experiment?

The steps in the review process are 1) submission of relevant information on the proposed experiment to OBA, 2) publication of the proposal in the *Federal Register* for 15 days of comment, 3) review by the RAC at a public meeting, and 4) approval by the NIH Director who stipulates the containment conditions and any special requirements for the experiments.

6. Does the IBC need to review the proposal before it is sent to OBA?

The IBC may initiate its review of these experiments before or after submission to OBA and review by the RAC. The IBC's final determination should occur after this process, because the IBC must take into account any special conditions that the NIH Director (or OBA) has stipulated as a condition of approval and ensure that they are implemented. Research that meets the criteria for Section III-A-1-a cannot be initiated unless approval is granted by the NIH Director (or OBA in the case of an equivalent experiment). See question 9.

7. What information needs to be submitted to OBA for review of research that involves the transfer of drug resistance that may ultimately be reviewed and approved by the NIH Director?

Information about the proposed experiment that OBA requires to determine whether the experiment meets the criteria of Section III-A-1-a of the *NIH Guidelines* includes 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, and other pertinent characteristics of the recombinant construct).

If the experiment is considered to be a III-A-1-a experiment 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 disease caused by the organism in question. This should include a statement whether the submitting investigator or others have considered any alternatives.
- A description of the proposed risk mitigation strategies that will be implemented to minimize risk to laboratory personnel as well as to the public.
- Minutes, if available, of any IBC discussion of the research in question (IBC review is not required prior to RAC review and NIH Director approval, but a preliminary review is desirable).
- IBC contact information.

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

- Description of the biosafety features of the room(s) in which the research will be conducted.
- Most recent inspection report(s) of the room(s) in which the research 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 laboratory personnel will receive specific to the research question.
- Description of any special occupational health requirements for the laboratory personnel involved in the research (e.g., vaccination, medical surveillance).

Submission of relevant information on a proposed Section III-A-1-a experiment should be made to:

Office of Biotechnology Activities
National Institutes of Health
6705 Rockledge Drive, Suite 750
Bethesda, MD 20892-7985 (20817 for non-USPS mail)
Telephone: (301) 496-9838
Fax: (301) 496-9839
Email: oba@od.nih.gov

8. Who approves Section III-A-1-a experiments?

The NIH Director approves these experiments after consideration of the RAC's recommendations and any public comments. These experiments may not proceed unless approved by the NIH Director and the IBC.

9. Once a Section III-A-I-a experiment has been approved by NIH, do equivalent experiments also need to be reviewed by the RAC and approved by the NIH Director?

Once a Section III-A-I-a experiment has been reviewed by the RAC and approved by the NIH Director, equivalent experiments may not need to follow the same approval process to determine the appropriate biosafety containment level for the work. Under Section III-B-2 of the *NIH Guidelines* (Experiments that Require OBA and IBC Approval Before Initiation), OBA may determine that a proposed experiment is equivalent to one that has previously been approved by the NIH Director as a Major Action. An experiment will be considered equivalent only if, as determined by OBA, there are no substantive differences in methodology and other pertinent information has not emerged since submission of the initial III-A-1-a experiment that would change the biosafety and/or public health considerations for the proposed experiment. If OBA makes such a determination, experiments deemed to be equivalent will not require review and approval under Section III-A-1-a. These experiments will have been approved by OBA and may proceed once approved by the appropriate IBC.

10. My research involves the transfer of a drug resistance trait into an organism on the Department of Health and Human Services (HHS) and/or the United States Department of Agriculture (USDA) Select Agent list (i.e. is a "restricted experiment") and thus requires approval from those agencies. Do I also need to submit a request to OBA for approval?

Experiments utilizing recombinant or synthetic nucleic acid molecules that involve the deliberate transfer of a drug resistance trait into a Select Agent (that meet the definition of a restricted experiment) may be subject to the regulatory authority of, and review by, HHS and/or USDA under their respective rules (found 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) supersedes the requirement for RAC review and NIH Director approval under the *NIH Guidelines*. However, other provisions of the *NIH Guidelines* - for example, IBC review and approval - are still applicable.

11. I am conducting research that involves the transfer of resistance to certain drugs in a strain of a Select Agent that has been excluded or exempted from the Select Agent regulations. From which agency do I need to get approval?

Potential III-A-1-a experiments in strains of Select Agents that have been excluded or exempted from the Select Agent regulations should be submitted to OBA.

Useful Links and Resources Regarding the Control of Disease Agents

Government Resources

PubMed:

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

Centers for Disease Control and Prevention:

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

World Health Organization:

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

Medline:

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

Private Resources (fees may apply)

Up to Date Online

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

Control of Communicable Diseases Manual

Editor: David L. Heymann

Publisher: American Public Health Association

ISBN-13: 978-0875530345

Johns Hopkins ABX Guide

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

Red Book: Report of the Committee on Infectious Diseases

Publisher: American Academy of Pediatrics

ISBN-13: 978-1581101942

Sanford Guide to Antimicrobial Therapy 2011 (or updated editions)

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

Publisher: Antimicrobial Therapy

ISBN-13: 978-1930808300

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

Principles and Practice of Pediatric Infectious Disease

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

Publisher: Saunders

ISBN-13: 978-0443066870

Merck Manual

<http://www.merckmanuals.com/professional/index.html>

RAC discussions of Major Actions involving the transfer of drug resistance:

http://oba.od.nih.gov/rdna_rac/rac_meetings.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*

December 2009 RAC Meeting: Transfer of tetracycline resistance to *Chlamydia trachomatis*