

Introduction of Drug Resistance Traits Under the *NIH Guidelines*

Jacqueline Corrigan-Curay, J.D. M.D.
Acting Director
Office of Biotechnology Activities



June 23, 2009



Panel III: Introduction of Drug Resistance: Section III-A-1

Moderators

**Louis Kirchhoff, M.D., University of Iowa
Dennis Dixon, Ph.D., NIAID, NIH**

Panelists

**Ronald Atlas, Ph.D., University of Louisville
William Bishai, M.D., Ph.D., Johns Hopkins School of Medicine
Stanley Maloy, Ph.D., San Diego State University
Andrew Onderdonk, Ph.D., Harvard Medical School
Louis Rice, M.D., Case Western Reserve University
Alfredo Torres, Ph.D., University of Texas Medical Branch**

Overview

- ❑ Which experiments involving introduction of drug resistance need to be reviewed by the Recombinant DNA Advisory Committee (RAC) and approved by the NIH Director – Section III-A-1 experiments
- ❑ Recent III-A-1 Experiments
- ❑ Proposed Amendments

Current *NIH Guidelines*:

Section III-A-1

- Introduction of drug resistance into a microorganism if:**
 - Not known to acquire the trait naturally; and**
 - Acquisition of the drug resistance could compromise the use of the drug to control disease in humans, animal and plants.**

Public Health and Scientific Research

- ❑ **The deliberate creation of a microorganism that may be more difficult to manage or treat creates a public health risk**
- ❑ **This public health risk is not only of local concern and warrants a more thorough in-depth review, expert consultation and public discussion in the context of the RAC.**

Public Health and Scientific Research

- **If there is a potential public health benefit to the research, how best to protect public health in the short term without impeding long term benefits of research?**

Public Health and Scientific Research



- ❑ **The III-A-1 review process involves a public, transparent review of experiments that raise important public health issues**
 - **Potential scientific and public health benefits of the research**
 - **Evidence on the availability of alternative markers**
 - **Risks to public and to lab workers**
 - **Utility of the drug in treatment and management of disease**
 - **If the experiment is allowed to proceed, how can the risks be minimized?**

Clinical Utility Assessment

- ❑ **What are the currently recommended treatments for the disease caused by the organism?**
 - Evidence for clinical efficacy
 - Side effect profile
 - Affordability and availability (in the U.S. and abroad)

Clinical Utility Assessment

- ❑ **Is this drug considered first or second line?**
 - **If the organism is made resistant to this drug how many alternative drugs would be available?**
 - **Is there the possibility of causing cross-resistance to other drugs in the same or different classes?**

- ❑ **Even if not first or second line, is this drug indicated in certain populations (e.g. pregnant women, children) or used as first line therapy in other countries?**

Special Populations

- ❑ ***Borrelia burgdorferi* - insertion of erythromycin resistance as a marker**
 - Oral antibiotics of choice: doxycycline, ampicillin or cefuroxime
 - Pediatric patients and pregnancy:
 - doxycycline contraindicated
 - ampicillin or cefuroxime available but what about if severe PCN allergy?
 - Macrolides not first-line but recommended for patients intolerant to amoxicillin or cefuroxime

Major Actions Reviewed by RAC

- ❑ **1992: Tetracycline resistance into *Porphyromonas gingivalis***
- ❑ **1993: Chloramphenicol resistance into *Rickettsia prowazekii****
- ❑ **2007: Tetracycline resistance into *Chlamydia trachomatis***
- ❑ **2007: Chloramphenicol resistance into *Rickettsia conorii* and *R. typhi***

* Did not complete review process

Tetracycline Resistance into *Chlamydia trachomatis*

- ❑ Doxycycline is a first line antibiotic, but there are alternatives**
- ❑ Public health benefit to research on these strains and few markers available**
- ❑ Approval specific to investigators and to genital strains, since the eye disease caused by other strains is treated with tetracycline**

Chloramphenicol Resistance and *Rickettsia conorii* and *R. typhi*

- ❑ Doxycycline is a first line antibiotic
- ❑ Chloramphenicol second line and rarely used in the U.S. but often first line in developing countries
- ❑ Emerging data for fluoroquinolones, especially for *R. conorii*

Chloramphenicol and Rickettsia

- RAC Recommendation:

Proceed in *R. conorii* first and once established that chloramphenicol is a useful marker will then reconsider *R. typhi*

Questions Considered

- ❑ **Should the lack of documented resistance to the drug in the community be the primary criterion for determining what needs to be reviewed?**
 - **What if there are only 1 or 2 antibiotics available and there is only a low level of resistance?**
 - **What if the drug resistance marker is for a drug used primarily to treat children?**

Discussion Questions

- ❑ **At what point does one consider that an organism “can acquire the trait naturally”? Is a single case report sufficient? What if there is no documented resistance in the United States?**
- ❑ **Are there other objective criteria that could be used to better capture those experiments that have potentially significant public health implications?**

Discussion Questions

- ❑ **How do we address special populations, e.g., pregnant women, children, and health care systems with more limited resources?**

Should these Experiments be Reviewed?

- ❑ Ciprofloxacin resistance into *Neisseria meningitidis*
- ❑ Vancomycin resistance into *Staph. aureus*
- ❑ Ceftriaxone resistance into *Neisseria gonorrhoeae*
- ❑ Pyrimethamine resistance into *Toxoplasma gondii*

Special Populations

- ***Typhoid Fever: S. enterica typhi***
 - Antibiotic of choice: Ciprofloxacin
 - If Cipro resistance, 3rd generation cephalosporins or azithromycin

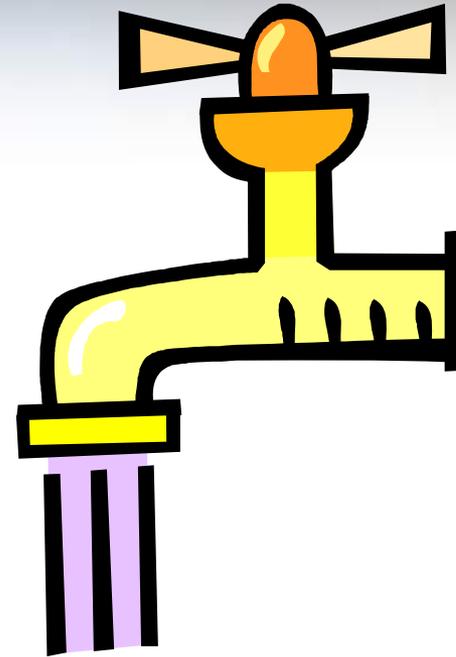
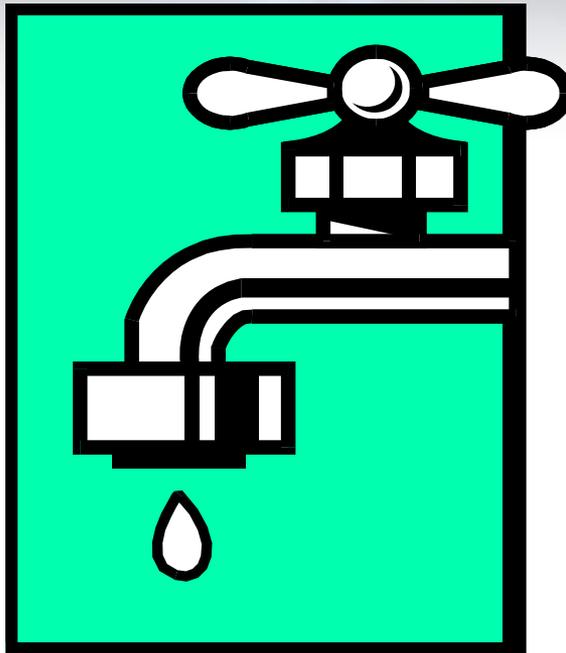
 - Chloramphenicol used in developing countries
 - Certain areas of South America and sub-Saharan Africa with limited resistance
 - Emergence of chloramphenicol sensitive strains in India as fluoroquinolones use increased

 - If Chloramphenicol used extensively outside U.S. for typhoid fever should chloramphenicol resistance be used as a marker for *S. enterica typhi*

Proposed Language

- ❑ **The deliberate transfer of a drug resistance trait to microorganisms, if such acquisition could compromise the ability to treat or manage disease agents in human and veterinary medicine or agriculture, will be reviewed by RAC**
- ❑ **Even if an alternative drug or drugs exist for the control or management of disease, it is important to consider how the research might affect the ability to control infection in certain groups or subgroups by putting them at risk of developing an infection by such microorganism for which alternative treatments may not be available. Affected groups or subgroups may include, but are not limited to: children, pregnant women, and people who are allergic to effective alternative treatments, immunocompromised or living in countries where the alternative effective treatment is not readily available.**

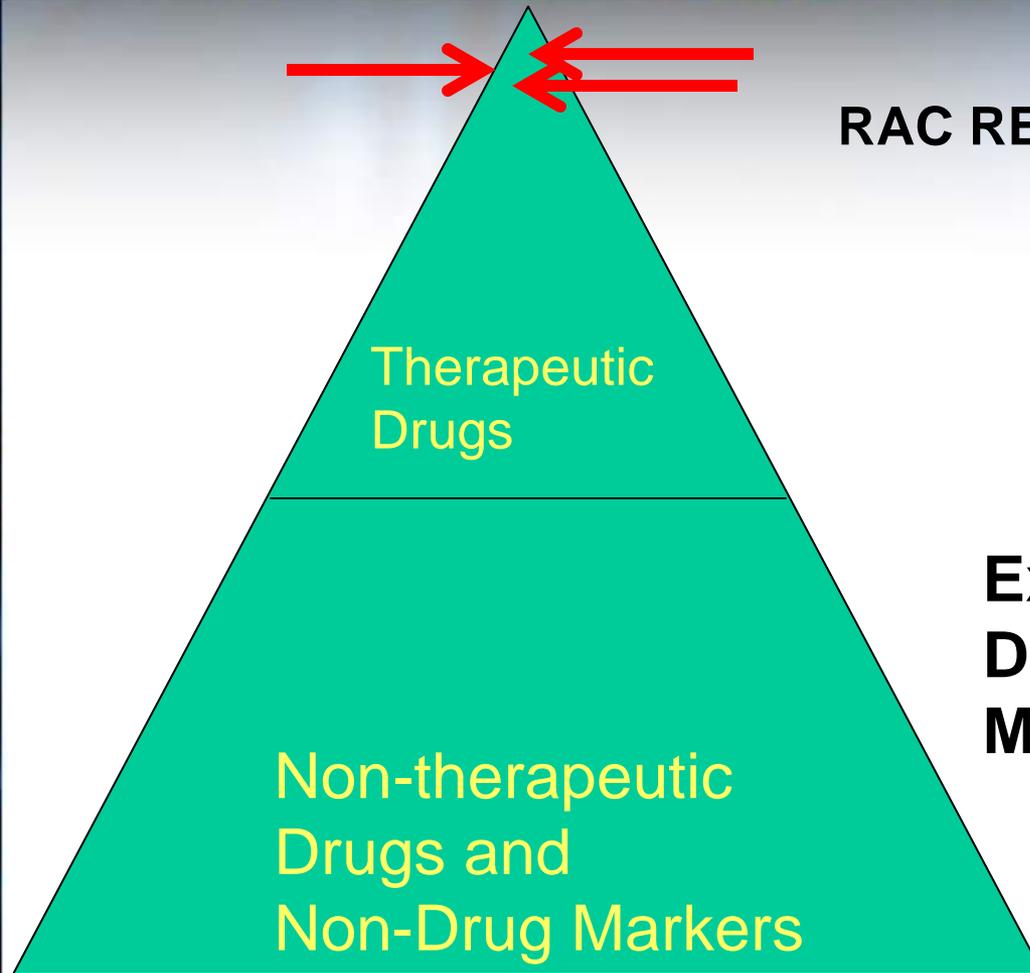
The Response



Non-III-A Experiments

- Any drug resistance into an organism that does not cause disease. This would include common non-pathogenic prokaryote and lower eukaryote **host-vector systems** (e.g. *E. coli* K12, *E. coli* B, *Saccharomyces* etc...) either listed in Appendix E or **vector systems** that meet the biological containment criteria described in Appendix I of the *NIH Guidelines*
- Use of a drug resistance marker for a drug that cannot be used empirically due to resistance
 - Methicillin resistance into *S. aureus*
 - Ampicillin in pathogenic strains of *E. coli*

Finding the Right Balance



RAC REVIEW REQUIRED

**Experiments using
Drug Resistance
Markers**

