It All Starts in a Lab! Laboratory Issues and the Research Regulatory Environment

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Los Angeles Times

Deadly UCLA lab fire leaves haunting questions

Problems at UCLA went unfixed for two months before a young researcher was burned in a chemical accident.

March 01, 2009|Kim Christensen
At http://articles.latimes.com/2009/mar/01/local/me-uclaburn1

Presentation Overview

- Review of Major Lab Standards & Regulations
- Scenarios for Discussion
  - "Set Time Machine to 1918!"
  - "The Case of the Disappearing PI"
  - Mousepox

Review of Major Lab Standards & Regulations

Occupational Health & Safety

- OSHA – Federal v. State OSHA Plans
- General Duty Clause (29 USC Sec. 654)
- Personal Protective Equipment (PPE) (29 CFR 1910.132)
- Occupational Exposure to Hazardous Chemicals in Laboratories (29 CFR 1910.1450) -- Chemical Hygiene Plan
- Bloodborne Pathogens Standard (29 CFR 1910.1030)
- Hazard Communication Standard (29 CFR 1910.1200)

Challenges

- Enforcement of industrial-type standards in an academic setting.
- Hazard assessment and training across multiple different types of research and different audiences.

Biosafety

- CDC's Biosafety in Microbiological and Biomedical Laboratories (BMBL)
  - Risk Assessment and Containment
  - Establishment of Biosafety Levels BSL-1 to BSL-4
  - Summary Statements and BSL levels for particular agents

Challenges

- Process/committee for protocol review and correct assignment of BSL level.
- Ensuring that protocol modifications are reviewed before they take place.

Recombinant DNA

- NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules
- Recombinant DNA Advisory Committee (RAC)

Institutional Biosafety Committee

Purpose of the IBC

- Review research with recombinant DNA (rDNA).
- Institutions that receive support from the National Institutes of Health (NIH) for rDNA research are required to establish and register an Institutional Biosafety Committee (IBC) with the NIH Office of Biotechnology Activities (OBA) in compliance with the *NIH Guidelines for Research Involving Recombinant DNA Molecules (NIH Guidelines).*

Institutional Biosafety Committee

- The IBC investigates and reports any significant problems with or violations of the *NIH Guidelines* and any significant research-related accidents or illnesses involving recombinant genomic materials to the Principal Investigator, the Biological Safety Officer, the Department Chair, and the NIH Office of Biotechnology Activities (OBA) within 30 days.

Challenges

- Reporting incidents to NIH within time limits.
- Capturing dual use research of concern on the registration forms and training principal investigators.
- The case of the Jumping Mice
  - How to be on a first name basis with NIH OBA

Federal Select Agent Program

42 CFR Part 73

- Select agents are biological agents and toxins that have been determined to have the potential to pose a severe threat to public health and safety, to animal and plant health, or to animal or plant products
- Regulators: CDC (42 CFR Part 73 & USDA (7 CFR Part 331; 9 CFR Part 121)
- Inspection of programs every 3 years

Challenges

- Labor intensive programs – personnel, training, documentation.
- Heavily regulated and subject to public scrutiny.
- Rapid response to and reporting of incidents/accidents in BSL 3 or 4 lab (e.g., needle sticks, escaped infected animal, reversal of airflow, spills).
  - Immediate reporting and follow-up in 7 days.
  - Communication with counsel and compliance office is essential.

Shipping

Domestically/International

49 CFR Parts 171-177: Hazardous Materials Regulations (DOT)

- Who needs to be certified:
  - prepares,
  - classifies,
  - packs,
  - labels,
  - or offers a dangerous good for transport.
  - Certification is good for **2 years**
  - $37,500 per violation if caught vs. self disclose

Challenges

- Surprise visits by Federal Aviation Administration (FAA) and Department of Transportation (DOT).
  - They work in collaboration with FedEx and other freight forwarders
- Inspection of training and shipping records along with packaging material.
  - Mislabeled packages may be cause for enforcement, e.g., antibodies from China labeled as “Christmas Toys.”

Importing Animal and Plant Material

- When importing animal material many times an Animal Plant and Health Inspection Services (APHIS) permit is required
- This drives an inspection from the authorities
- Users have to be trained to meet the conditions of the permit to be in compliance

Importing Human Material

- When importing human or material a Centers for Disease import is needed in most cases
- Users have to be trained to meet the conditions of the permit to be in compliance

Challenges

- Ensuring that permits are applied for in advance.
- Educating researchers about the potential for fines and detention by customs officials.

Export Controls

- Exports and Deemed Exports
- International Traffic in Arms Regulations (ITAR)
  - State Dept.
  - Designed or intended for military end-use
- Export Administration Regulations (EAR)
  - Bureau of Industry & Security, Dept. of Commerce
  - Dual Use -- primary commercial application + potential for military or weapon use

Exporting

Export Administration Regulations (*EAR*), *15 CFR* §§730-774 U.S. Department of Commerce.

- If you are exporting outside the U.S. any of the following items you need to be concerned with export control laws:
  - Laboratory Equipment
  - Viruses
  - Bacteria
  - Toxins
  - Genetic Elements of Pathogens

Challenges

- Export policy & training
  - Education on when licenses are required.
  - Required reporting of illegal exports.
- Identifying international projects that receive exports.
- Shipment tracking.
- Application for licenses.

Challenges

- Deemed Exports
  - Where are non-US citizens/permanent residents working?
- Fundamental Research Exclusion
  - Who is making sure exclusion is preserved?
- I-129 Deemed Export Certification
- Visits from Dept. of Commerce.

Dual Use Research (DUR)

- Research that has the potential to be misused for nefarious purposes is said to be “dual-use.”
- Most life science research has some potential for misuse and therefore falls under DUR category.

Dual Use Research of Concern (DURC)

*The National Science Advisory Board for Biosecurity (NSABB) has defined Dual Use Research of Concern (DURC) as: *"research that, based on current understanding, can be reasonably anticipated to provide knowledge, products, or technologies that could be directly misapplied by others to pose a threat to public health and safety, agricultural crops and other plants, animals, the environment or materiel"*. *NSABB 2004

Dual Use Research Concern

Focuses on research that involves certain agents or toxins, e.g., ebola, anthrax, marburg, botulism, plague, etc.

Seven categories of experiments that meet DURC:

- **Enhances the harmful consequences of an agent or toxin.**
- **Disrupts the immunity or the effectiveness of an immunization without clinical and/or agricultural justification.**
- **Confers to the agent or toxin, resistance to clinically and/or agriculturally useful prophylactic or therapeutic interventions against that agent or toxin or facilitates their ability to evade detection methodologies**
- **Increases the stability, transmissibility, or the ability to disseminate a biological agent or toxin.**
- **Alter the host range or tropism of the agent or toxin**
- **Enhance the susceptibility of a host population to an agent or toxin.**
- **Generates or reconstitutes an eradicated or extinct agent or toxin.**

Scenarios for Discussion

Scenario 1, Part 1: Set the Time Machine to 1918!

- Eddie Marretti, a foreign national that was born in Italy but has lived in China is a new graduate student in an influenza lab working with H1N1, and H2N2.
- Before working in the lab, Eddie did not know that you could buy flu genome sequences from a company call Genetech. He is planning to order some genetic sequences to see if he can reconstruct H5N1 Avian Influenza in his garage. He has told his friend Greg, a researcher at Big University, what he plans to do.

Scenario 1, Part 2

- Not wanting Eddie to get a jump on him, Greg calls his colleague Dr. Hu in China and asks him to send H1N1 samples Hu has been working on. Hu wraps up the samples in a silk shirt he planned to send Greg for his birthday and puts them in the mail. Greg receives the samples and uses the blood to infect two chickens that he was using on a different research protocol. Because he didn't have IACUC approval for this new research "just yet," he removed the chickens from the animal housing area to his lab.
- Hu also contacts Greg's grad student Ace Tester, who is in China at conference, and gives Ace some more samples to take back to Greg. Ace puts them in his shirt pocket and is detained by a US Customs agent who spies the test tubes. On testing, the samples are found to contain highly pathogenic avian influenza virus, a select agent. APHIS agents head to Greg's lab and the local press gets wind of the story and show up too. Lab workers around Greg's lab "feel sick" and head to the ER at Big University's hospital.

Scenario 2: The Case of the Missing PI

- Dr. Awol is the PI of a large laboratory at Elm University. Awol goes on a lecture tour and leaves his lab mgr., Dr. Newbie, in charge. Newbie is already moonlighting, so he delegates his new duties to post-doc Bob. Bob is supposed to take care of the expired certifications for the bio-safety cabinets. The vendor comes and Bob notices that he just puts stickers on the cabinets without testing them. The vendor tells Bob, "these things never break," so Bob doesn't worry.

Scenario 2, con't

- Undergrad Lisa tells Newbie she needs to work on a new experiment over the weekend. Newbie asks Bob to meet Lisa at the lab, give her safety training and stay with her while she does the work.
- Bob opens the lab, but then leaves for a date, telling Lisa to find on-line training.
- Lisa can't get the biosafety cabinet light to work, so she works at the bench with a liquid that contains a bacteria. She splashes it in her eye and immediately calls Newbie. Newbie says "it's not that dangerous" and "make sure you don't tell anyone you were alone, or we'll all get in trouble." 3 days later Lisa goes to urgent care with a very swollen eye, and she is immediately sent to the hospital, where she is admitted overnight to receive IV antibiotics.

Scenario 3, Mousepox

- Eastern University received NIH money to conduct a mousepox experiment- A strain of ectromelia virus (mousepox) was bioengineered in an effort to sterilize mice in Australia. Unexpectedly the strain killed 60% of the infected mice. (2001)
- The researcher published the results in *Mbio* without consulting Counsel or Compliance. Immediately upon publishing *USA Today* picked up the story and surprised the university by accusing them of being irresponsible for publishing dual use research results. Many in the research community feared that publication of this research would provide a blueprint for those with malevolent intentions and a more virulent strain of smallpox could be created to infect humans

Questions

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