Continuing Role of Animals in the Future of Life Sciences Research

FDA Perspectives

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My comments are an informal communication and represent my own best judgment.

These comments do not bind or obligate FDA.
Themes

• FDA would not be able to make regulatory decisions without well-designed, scientifically valid studies in animals
• How FDA supports application of the 3Rs principles
• Future Trends
FDA would not be able to make regulatory decisions without well-designed, scientifically valid studies in animals

- Animal models of human disease are critical for discovery, development, and evaluation of novel medical products

- In general, animal studies are required for proof-of-concept and toxicity evaluation of regulated products; informs dosing (i.e., PK/PD)

- In some instances, such as medical countermeasures, efficacy studies cannot ethically be performed in humans and will require use of animal models.
FDA Research and Regulations

• Nonclinical safety or toxicity studies conducted to support approval and marketing decisions for products regulated by the FDA must be conducted in accordance with Good Laboratory Practice Regulations (21 CFR Part 58)
• If those studies are conducted using a regulated species, the Animal Welfare Act and regulations also apply
• Studies funded by the US government must also comply with Public Health Service Policy on Humane Care and Use of Animals
“Animal Rule*: Requirements for Animal Efficacy Studies

• Reasonably well-understood pathophysiological mechanism
• Effectiveness in >1 animal species
• Animal study endpoint related to desired benefit in humans
• PK/PD data allows selection of an effective human dose

*21 CFR Parts 314 and 601: New Drug and Biological Drug Products; Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible
FDA scientists use a variety of animal models to support the regulatory science needs of the Agency.
Large Animal Research Facilities

- Milk and meat safety
- Biomarker research
- Aquaculture research
- Microbial resistance
- Cardiovascular disease research (CDRH)
### Overview of CVM Aquaculture Research

**Goals:**

1. To facilitate new drug evaluation for aquatic species (minor species)
2. To assist with the Agency’s surveillance efforts to protect the food supply from illegal drugs/chemicals in food fish.

**Studies Include:**

1. Developing disease models to test drug effects,
2. Efficacy testing,
3. Pharmacokinetic studies
4. Depletion studies of prohibited chemicals
5. Providing tissues incurred with drug residues for development of chemical detection methods.
Variety of Animal Models Used in Biologics/Drugs Regulatory Science Programs

- High throughput genetic screens
- Developmental biology studies
- Disease models
  Immune correlates of protection
  For vaccines
- Influenza virus
  Vaccine preparedness
- Disease models, vaccine studies
Addressing Immediate Public Health Needs Through Developing Model to Evaluate Needed New Vaccines

• Recently there has been a resurgence in whooping cough caused by *B. pertussis* (*The Pertussis Paradox: Science 341:455, August 2013*)

• CBER scientists developed a non-human primate model for this disease that should facilitate further vaccine development
How FDA supports application of the 3Rs principles

Identifying alternatives:

• FDA participates in ICCVAM, Tox-21 to support identification, validation and adoption of alternative approaches
• Investigating in vitro approaches for toxicology screens, such as organs-on-a-chip
• Lower phylogenetic species
• Use early endpoints to reduce suffering, when possible
Enrichment
ICCVAM Mission and Role

The Interagency Coordinating Committee on the Validation of Alternative Methods:

• To facilitate and promote development, validation and regulatory acceptance of new and revised regulatory test methods that:
  – Reduce, refine, and replace the use of animals in testing
  – Maintain and promote scientific quality and the protection of human health, animal health, and the environment

• Together with NICEATM, provides translational infrastructure for validation, evaluation, and regulatory acceptance of new regulatory safety tools
  – Serve critical role in moving science from the bench to approved regulatory safety tools

Adopted by ICCVAM February 2004
All of ICCVAM’s activities are grounded in the U.S. Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training
http://grants.nih.gov/grants/olaw/references/phspol.htm#USGovPrinciples
Poliovirus Monkey Neurovirulence Test

- **Monovalent bulks**
  - Type 1: $12 + 12 = 24$
  - Type 2: $12 + 12 = 24$
  - Type 3: $24 + 24 = 48$
  - Total = 96 monkeys

Each vaccine lot was tested twice: first by a manufacturer and then by the National control authority requiring close to 200 monkeys for release of one trivalent bulk.
Poliovirus Mouse Neurovirulence Test

- Type 1: $32 + 32 = 64$
- Type 2: $32 + 32 = 64$
- Type 3: $32 + 32 = 64$
- Total = 192 mice

- Endpoint is mild neurological signs such as difficulty walking, grasping

Transgenic PVR Tg-1 mice for testing of poliovirus type 3 neurovirulence: comparison with monkey test.

Future Trends

• Improved telemetry and non-invasive imaging to use fewer animals/more precise information from in-life measurements

• More predictive models, i.e., humanized mice that better recapitulate human disease/response

• As improve mechanistic understanding, may support move to alternative approaches that will promote good animal welfare and scientific outcomes

• Improved in vitro and in silico approaches
In-Life Imaging Modalities to Reduce and Refine Use of Animals in Studies

Stages of Anthrax Infection in vivo using IVIS

Stage I  Stage II  Stage II/III  Stage III

Courtesy of Tod Merkel, CBER
Chimeric Mouse Model for the Propagation of Hepatitis C Virus
MUP/uPA Mouse Livers

Engrafted with human liver

A

Immunostained for Hu Alb

B

C

Not engrafted

D

Engrafted and Infected Mice are Positive for HCV RNA

H & E

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Research in Animals is a Critical Component Required for FDA’s Regulatory Science Program, as well as to Support Regulatory Decision-Making

Humane, well-designed, controlled studies are necessary when using animals in research and to support regulatory actions

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