The Reduction of Animal Use in Regulatory Testing

FDA Science Board
Advisory Committee Meeting

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People for the Ethical Treatment of Animals (PETA)

- Founded in 1980, PETA is a 501(c)(3) non-profit that has grown to 800,000 members worldwide, with a budget of ~$30 million and over 300 staff in offices in Norfolk VA (headquarters), Washington DC, New York, San Francisco, Los Angeles, UK, Germany, India, and Asia-Pacific

- **Areas of concern:** *animals used for experimentation*, animals raised for food, animals raised for their skins, animals used for entertainment

- **We work through:** *partnerships with industry and government*, public education, cruelty investigations and whistleblowers, animal rescue

Animal experimentation

- Decades-old tests that could not be validated today

- Not reliably predictive of human responses, esp. for different patient populations
    - Species variation and extrapolation
    - Poor disease models
    - Confounding effects of laboratory confinement, stress, environment, food, and so on
    - Reliability/reproducibility

- Expensive, time-consuming, and not amenable to high throughput

- Attempting to translate research from animals to humans not as efficient as studying humans directly

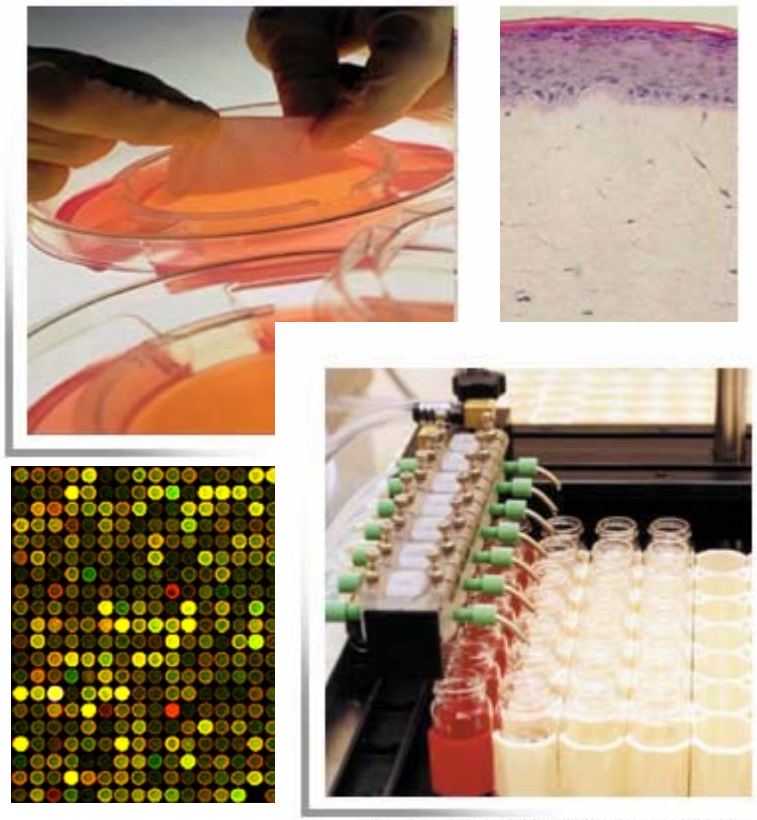
Human-based development of medical products

Target discovery

- Genomics/proteomics profiles of human tissues (e.g., diseased vs. normal)
- Epidemiology with genetic analysis

Safety and efficacy testing

- *In vitro* technologies (tissue cultures, physicochemical)
- Genomics/proteomics/imaging biomarkers in experimental medicine trials
- Predictive toxicology based on human molecular biology & chemical databases, QSARS, computer modeling and simulation



Advantages of modern human-based *in vitro* technologies

- Faster results
- Less expensive
- Greater repeatability/reproducibility
- Able to be automated/labor-saving
- Amenable to high throughput
- Species-relevant and thus more predictive (if developed correctly)
- Enable earlier incorporation of safety testing, and thus better portfolio management
- Less paperwork/doesn't require animal care and use committee approval
- Less exposure of personnel to animals and diseases
- More humane/less controversial

The costs of animal research to human health

Missed opportunities

- "How fortunate we didn't have these animal tests in the 1940s, for penicillin would probably never have been granted a license, and possibly the whole field of antibiotics might never have been realized." – Sir Alexander Fleming

Missed problems

- COX-2 inhibitors were found in animal studies to have a *protective* effect on cardiovascular health

Misleading

- "The history of cancer research has been a history of curing cancer in the mouse. We have cured mice of cancer for decades, and it simply didn't work in humans."
  - Dr. Richard Klausner, former Director of National Cancer Institute

Species differences in predictions of chemically induced birth defects[1]

	Mouse	Rat	Rabbit	Hamster	Primate	Dog	Cat
Butyl benzyl phthalate	+	+	–				
Mono benzyl phthalate	+	–	–				
Carbaryl	±	–	±	–	–	+	
Diazinon	–	+	–	–		+	
Dieldrin	+	±	–	+		–	
Diethylstilbestrol (DES)	+	–	–	–	–		
Lead acetate	–	+	–	+	+		
Methyl mercury	+	+	+	+	–	+	+
PCBs	–	–	–		±	+	

[1] Evidence of harmful effects (+), no evidence of harmful effects (–), or equivocal evidence (±)

Source: Schardein JL. *Chemically Induced Birth Defects*, 3rd Ed. Rev, 1109 pp. New York: Marcel Dekker (2000).

Further scientific examination and debate

- "…a comparison of data from rabbit tests and four-hour human skinpatch tests for 65 substances found that 45 percent of classifications of chemical irritation potential based on animal tests were incorrect."

  (MK Robinson et al., *Food Chem Toxicol* 2002; 40: 573-592)

- In a paper titled "Where is the evidence that animal research benefits humans?" researchers from Yale and British universities analyzed systematic reviews of animal research literature and concluded that

  "Clinicians and the public often consider it axiomatic that animal research has contributed to the treatment of human disease, yet little evidence is available to support this view…."

  They called for urgent formal evaluation of animal-based medical research. (Pound et al., BMJ 2004; 328:514-517)

Animals in the "critical path"

Assessing Safety

• Animal toxicology is "*laborious, time-consuming, requires large quantities of product, and may fail to predict the specific safety problem that ultimately halts development*." (Critical Path report, 3/04)

• ADMET problems responsible for 60-90% of drug failures

• Toxicogenomics and *in silico* predictive toxicology identified by CP report as best opportunities

Demonstrating Medical Utility (efficacy)

• "*Currently available animal models… have limited predictive value in many disease states.*" (Critical Path report, 3/04)

• Attempting to improve poor animal models is a relative waste of resources.

Industrialization (manufacturing)

• A bigger emphasis on advanced engineering principles and control technologies, GMP, and in-process characterization procedures and standards should be coupled with a reduction of requirements for quality control tests in animals (especially routine batch testing of biologicals)

International harmonization

- International Council for Animal Protection (ICAP)
  - A coalition of animal advocacy organizations based in Europe, North America, and Asia, representing 30 million supporters
- ICAPO (Int'l Council for Animal Protection in OECD Programmes)
  - "Invited expert" status at OECD since May 2002
  - Participates in meetings and provides technical comments on chemicals test guidelines
- Int'l Conference on Harmonization (ICH)
  - ICAP currently seeking observership
  - Need greater incorporation of the "3Rs" (reduction, refinement, and replacement of animal testing) into ICH guidelines
- EU legislation → harmonization issues around animal testing
  - EU will not accept animal tests when validated alternatives exist
  - 7th Amendment to the Cosmetics Directive: EU ban on animal testing of cosmetics ingredients (phasing in from 2009 to 2013)

Next steps

Guidances and regulations

- Incorporate validated non-animal technologies and delete corresponding animal tests

New alternatives

- Devote more FDA research and funding to validating and developing modern non-animal technologies (and/or work with NIH to direct funding)

Meetings

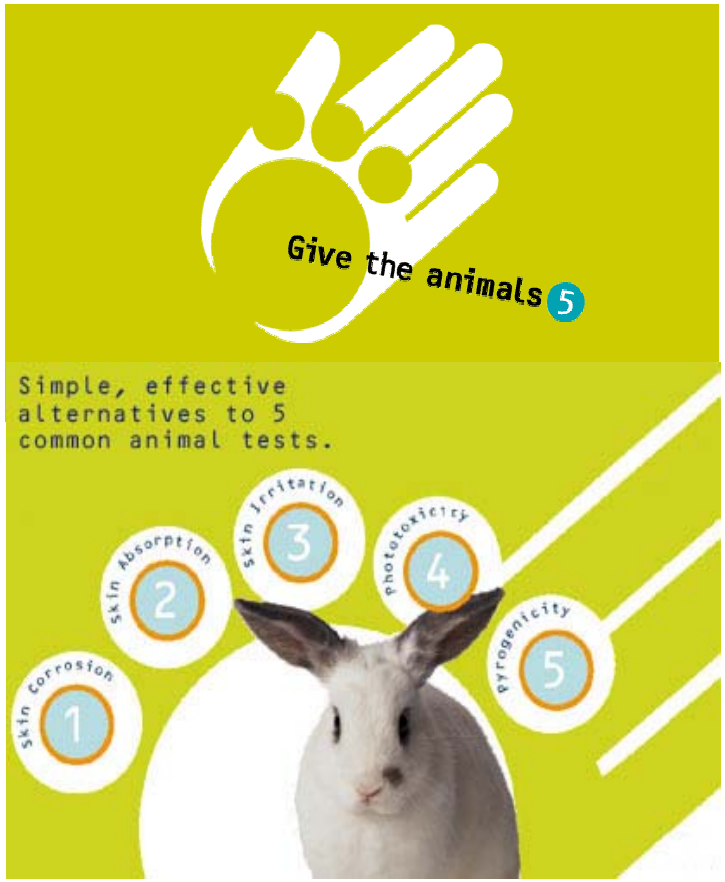
- Organize FDA workshops on animal testing alternatives including all stakeholders (gov't, industry, academia, animal protection organizations)
- Better familiarize FDA reviewers/researchers with new technologies

Enlist animal protection community

- Place animal protection organization staff scientists and alternatives experts on FACA committees
- Help establish ICH observership status for animal protection coalition

PETA's priorities for FDA change

- Replace requirements for animal tests with internationally validated alternatives
  - PETA's "Give the Animals 5" campaign highlighting pyrogenicity, phototoxicity, skin absorption, skin irritation, skin corrosion
  - Routine vaccine batch testing (see following slides)
- Validate and accept other alternatives
  - *In vitro* ADME tests
- Develop tests for longer-term endpoints
  - Non-genotoxic carcinogenicity (needed for *in vitro* battery to replace 2 year rodent cancer bioassay)
  - Reproductive and other organ toxicities



Status of alternatives in common vaccines: bacterial vaccines

Type	Examples	Animal test	Alternatives (accepted by)
Toxoids	Tetanus	• Safety: absence of toxin, irreversibility of toxoid, specific toxicity • Potency: multidilution vaccination challenge on guinea pigs or mice	• Deletion of specific toxicity test (EU) • Combined absence and irreversibility of toxin tests (EU) • *In vitro* endopeptidase test for toxin detection has been developed but not validated • Single dilution test (EU) • Antibody estimation by ELISA or ToBI (EU, WHO)
	Diphtheria	• Safety: absence of toxin (5 guinea pigs for bulk lot), irreversibility of toxoid, specific toxicity •Potency: multidilution vaccination challenge on guinea pigs with ~ 20 control animals	• Deletion of specific toxicity test (EU) • Combined absence and irreversibility of toxin tests (EU) • *In vitro* Vero cell test for toxin detection (WHO) • Single dilution test (EU, WHO) • Antibody estimation by Vero cell test (WHO) – ELISA and ToBI have also been developed
	Acellular pertussis vaccines (ACPVs)	• Safety: absence of toxin (5 mice), irreversibility of toxoid (5 mice) • Potency: multidilution vaccination + serology on 6 groups of mice	• In vitro CHO clustering test can be done on bulk but not final lot • Single dilution test (EU)
Bacterins	Whole cell pertussis vaccines	• Safety: mouse weight gain test with 10 mice for testing specific toxicity • Potency: Kendrick test - multidilution vaccination and intracerebral challenge in 136 mice – large numbers of animals, severe distress, poor precision and reliability	• Modified to use 5 guinea pigs (EU) • *In vitro* alternatives include LAL pyrogen test (WHO) • Humane non-lethal endpoints (EU) • Aerosol challenge instead of intracerebral • Antibody estimation by whole cell ELISA (validated in 2000)
	Cholera	• Potency: multidilution vaccination + serology on 6 mice, guinea pigs, or rabbits	• This serology test is accepted by the EU
	Haemophilus type B conjugate	• Potency: multidilution vaccination + serology on 16 mice	• This serology test is accepted by the EU • Moving testing upstream: if final bulk testing is satisfactory, can omit potency testing of final lot

Status of alternatives in common vaccines: viral vaccines

Examples	Animal test	Alternatives (accepted by)
Rabies	• Safety: extraneous agent testing •Potency: NIH test (multi-dilution vaccination + intra-cerebral challenge test in up to 170 mice per batch)	• Cell culture test (WHO) + EU for vet vaccines • Humane endpoints (EU) • Single dilution (EU) • Vaccination + antibody estimation using 5 mice (EU) • Antigen quantification (WHO)
Hep A (inactivated) and Hep B (recombinant)	• Vaccination + serological test in mice or guinea pigs	• Antigen quantification (EU, WHO)
Inactivated Poliovirus (IPV)	• Multi-dilution vaccination + serology in at least 60 rats	• Molecular analyses, e.g., MAPREC for poliovirus type 3 (WHO) • Neurovirulence in transgenic mice for poliovirus type 3 (WHO)
Oral Poliomyelitis (OPV)	• Neurovirulence testing in over 80 monkeys by intra-spinal injection	• Molecular analyses, e.g., MAPREC for poliovirus type 3 (WHO) • Neurovirulence in transgenic mice for poliovirus type 3 (WHO)

Already not tested in animals: *Influenza (tested in eggs), Meningococcal and Pneumococcal (only need pyrogen test which can be done in vitro), Oral typhoid, Varicella, Measles, Mumps, Rubella*

Currently no alternatives available: *BCG (2 safety tests on 6 guinea pigs each)*

Not covered here: *Yellow Fever, Smallpox, Japanese Encephalitis, Anthrax*