

# The Reduction of Animal Use in Medical Product Development

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Advisory Committee Meeting

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## 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

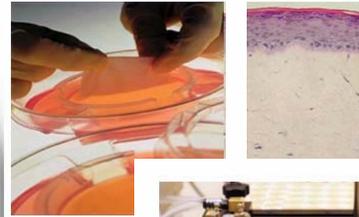


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## Human-based development of medical products

### 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



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## Update on Activities

### Regulators

- FDA (Science Forum, CDER meeting, Advisory Cmtee meetings)
- European Medicines Agency (EMA)

### Industry

- Meetings (J&J, Schering-Plough, Medtronic)
- Shareholder resolutions

### Academic meetings

- Invited speaker at Society for In Vitro Biology (SIVB)
- Invited speaker/poster presenter at 5<sup>th</sup> World Congress on Alternatives in Berlin

### International Conference on Harmonization

- Comments on S8 Safety Guideline on Immunotoxicity Studies
- Concept paper on Photosafety Studies
- Presented at FDA ICH prep meetings

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## Species Differences in Immune Systems

For humans the circulating leukocyte profile is 50-70% neutrophils but for rodents it is 50-100% lymphocytes. (Haley, 2003)

### *Relevance of measuring drug-induced alterations in animal leukocyte subset populations?*

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Mouse spleens are major sites for lifelong hematopoietic activity while humans have little hematopoietic activity in embryonic spleens and virtually none in adult spleens (Haley, 2003)

### *Relevance of using mouse spleen cells as target cells in immunotoxicity assays?*

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TCDD causes a dose-dependent suppression of the T-cell Dependent Antibody Response in adult female B6C3F1 mice, but *enhances* the TDAR in F344 and Long-Evans rats even at high doses. (Smialowicz et al., 1994)

### *Relevance to humans?*

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## Problems with Animal Testing for Cancer Therapies

- Animal tumors inherently different from human tumors
  - Grow more quickly and regress spontaneously
  - Generally of different types (e.g., sarcomas)
  - Species-specific mechanisms (e.g., saccharine)
- Induction of cancer in experimental animals is highly unnatural (chemical or radiation poisoning, tumor transplantation, targeted mutation)
  - Rb-defective mice don't show any signs of retinoblastoma
- Metabolism is significantly divergent between species, impacting both response to cancer-causing chemicals as well as chemotherapeutic drugs

“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

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## Animals in the FDA's "critical path"

**92%** of drugs that pass preclinical testing, currently almost all in vivo animal-based, now fail in clinical trials.

*"We must **modernize** the critical development path that leads from scientific discovery to the patient"* - Critical Path report, 3/04

### 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

### 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.

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## ICCVAM Authorization Act, 2000

**"Each Federal agency shall promote and encourage the development and use of alternatives to animal tests, including batteries of tests and test screens, where appropriate... for hazard identification or dose-response assessment purposes...."**

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## Rabies Vaccine Potency Testing

### NIH test

- 6-wk multi-dilution vaccination + intra-cerebral challenge test in ~ 600 mice per batch
- Control group dies of rabies
- Staff exposed to live rabies virus
- High degree of variability (25-400%)



### Antigen Quantification Test

- EIA directly measures 3D protective antigen
- Worked on in CBER labs
- Subject of 2003 WHO workshop
- Results cannot be correlated with highly variable NIH test



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## Carcinogenicity Testing

- 2-yr cancer bioassay in rodents widely acknowledged to be problematic
  - Test classifies > 50% of chemicals as carcinogens
  - Extremely burdensome in terms of time/resources (~\$1 million/study)
- Increasing challenging of 2-yr rodent cancer bioassay
  - American Council on Science & Health's book "America's War on Carcinogens" (1/05) and petition to EPA (8/05)
  - Society of Toxicology's The Great Debate (3/05): "The 2-yr Rodent Carcinogenesis Bioassay: Relevant or Relic?"
  - 9/05 ECVAM Invalidation Workshop
- Efforts to develop *in vitro* alternatives have not resulted in replacement
  - *In vitro* genotoxicity tests widely used *in addition to* rodent bioassay
  - Cell transformation assays (e.g., SHE assay, subject of OECD guideline)
  - What battery of *in vitro* tests can be developed to *replace* the rodent bioassay?

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## The Hurel Biochip

- Microfluidic circuits lined with cells from human organs
- Enables detection of interactions among multiple tissue types and compounds
- One version incorporates human uterine or colon tumor cells as well as healthy organ cells, testing for drugs with selective cytotoxicity
- Biochips based on a patient's cells will enable personalized medicine



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## Summary

- 92% failure rate is a crisis; Drug Safety needs to be addressed at preclinical stage as well as post-marketing surveillance.
- “It’s the best we have at this time” isn’t good enough.
- Getting “some information” from an invalid model isn’t better than no information at all.
- Making tissue models more physiological is more feasible than making animals into humans.
- We can’t transition to high-tech, human biology-based, effective R&D methods and personalized medicine in 50-100 years unless we take small concrete steps now.

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