



# DOD Research, Development, Translation, and Validation Activities Relevant to the NICEATM-ICCVAM Five-Year Plan

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The views expressed are those of the author and do not constitute endorsement by the Department of the Army.



MARINES



AIRFORCE

# SUPPORTING the WARFIGHTER



NAVY



ARMY



# Systems Biology

*"...the pluralism of causes and effects in biological networks is better addressed by observing, through quantitative measures, multiple components simultaneously and by rigorous data integration with mathematical models"*

Sauer, U. et al. (17 April 2007). "Getting Closer to the Whole Picture". *Science* **316**: 550.



# Telemetry Parameters

Electrocardiogram

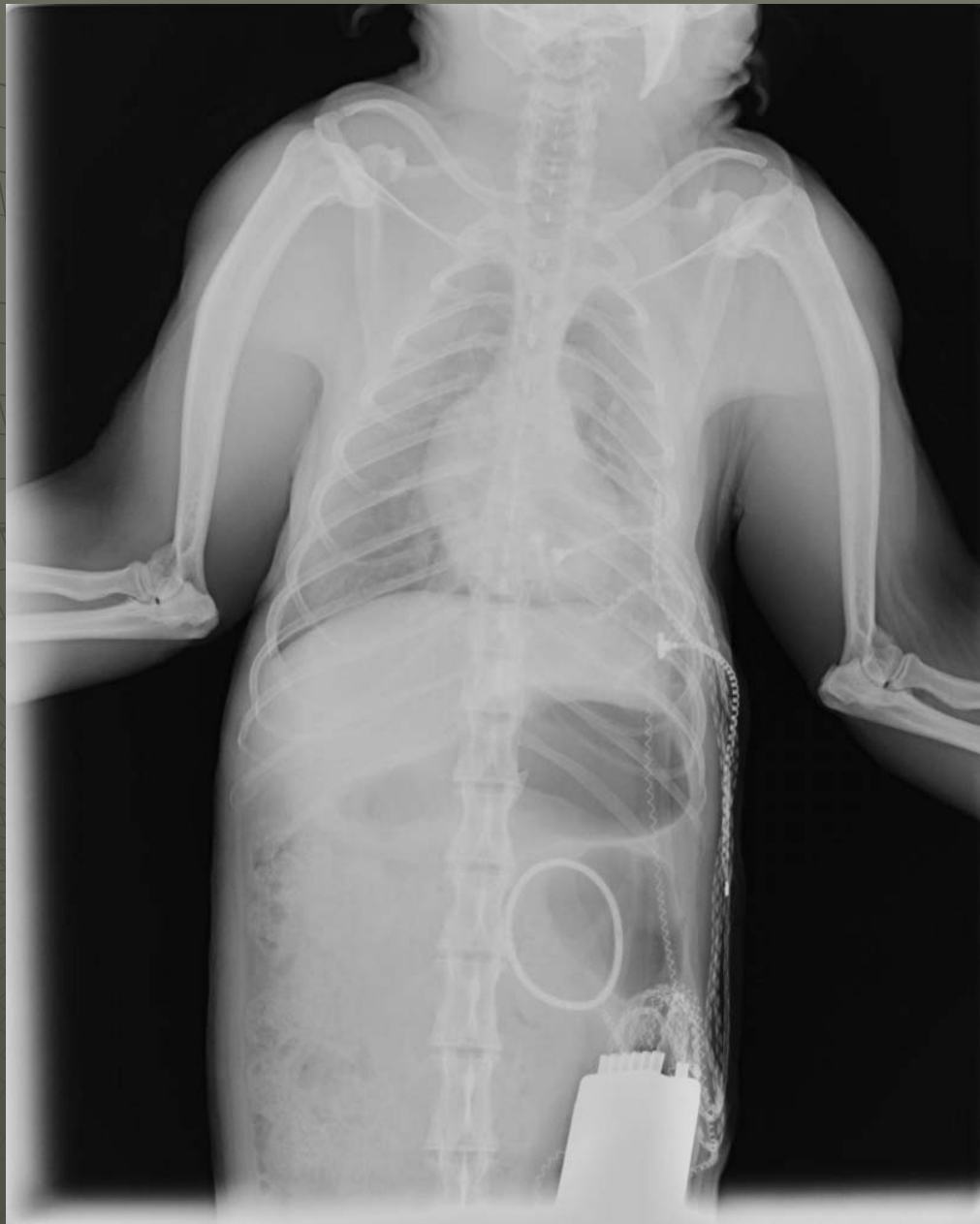
Ventricular/blood pressure

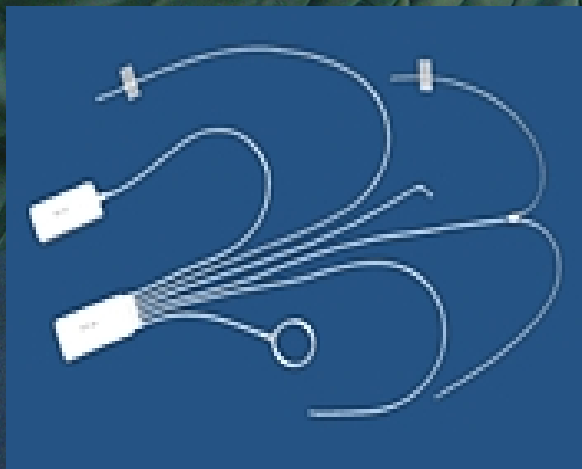
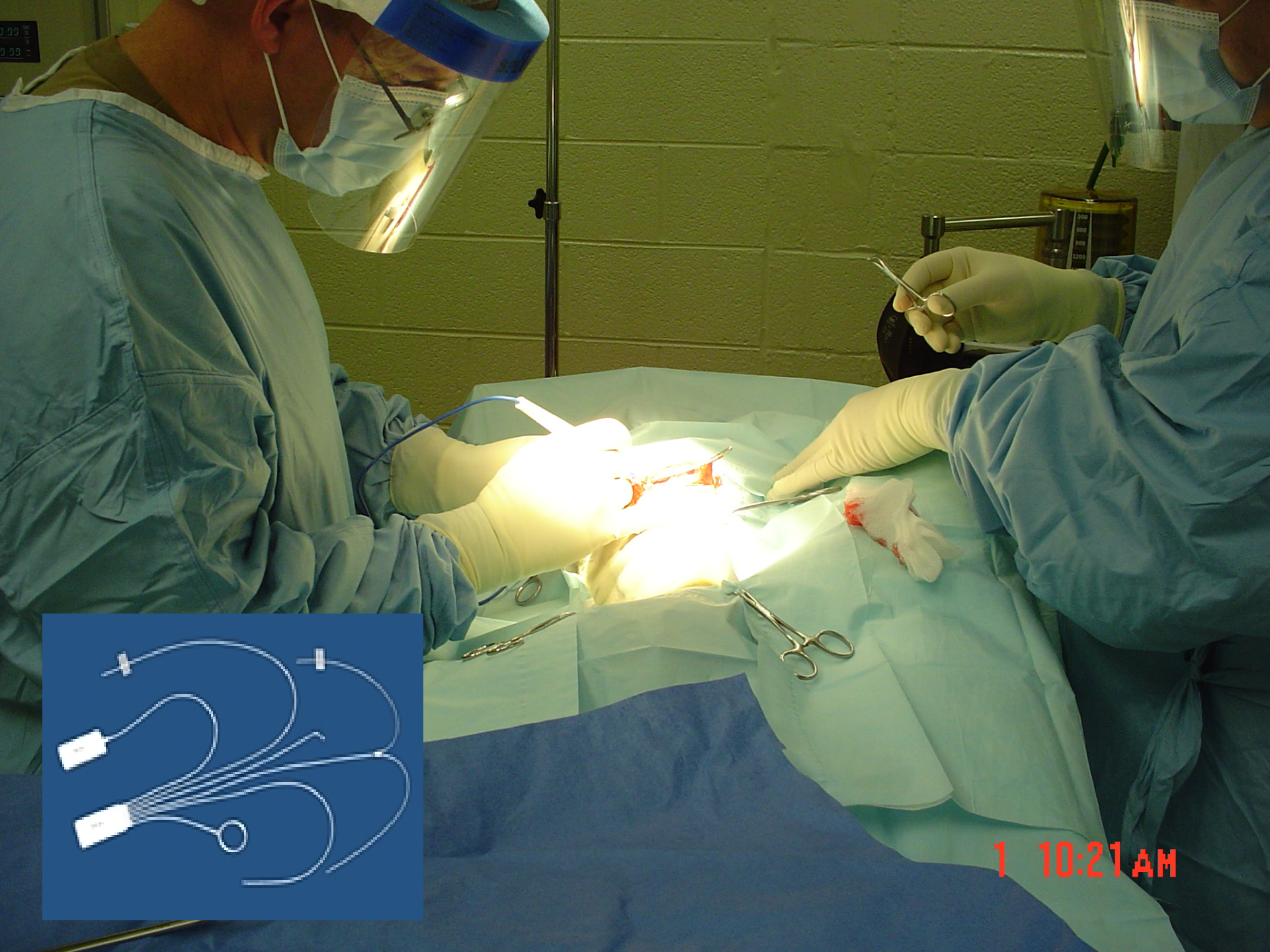
Intrathoracic pressure/respiratory  
parameters

Temperature

Activity

Detailed data for FDA packet!



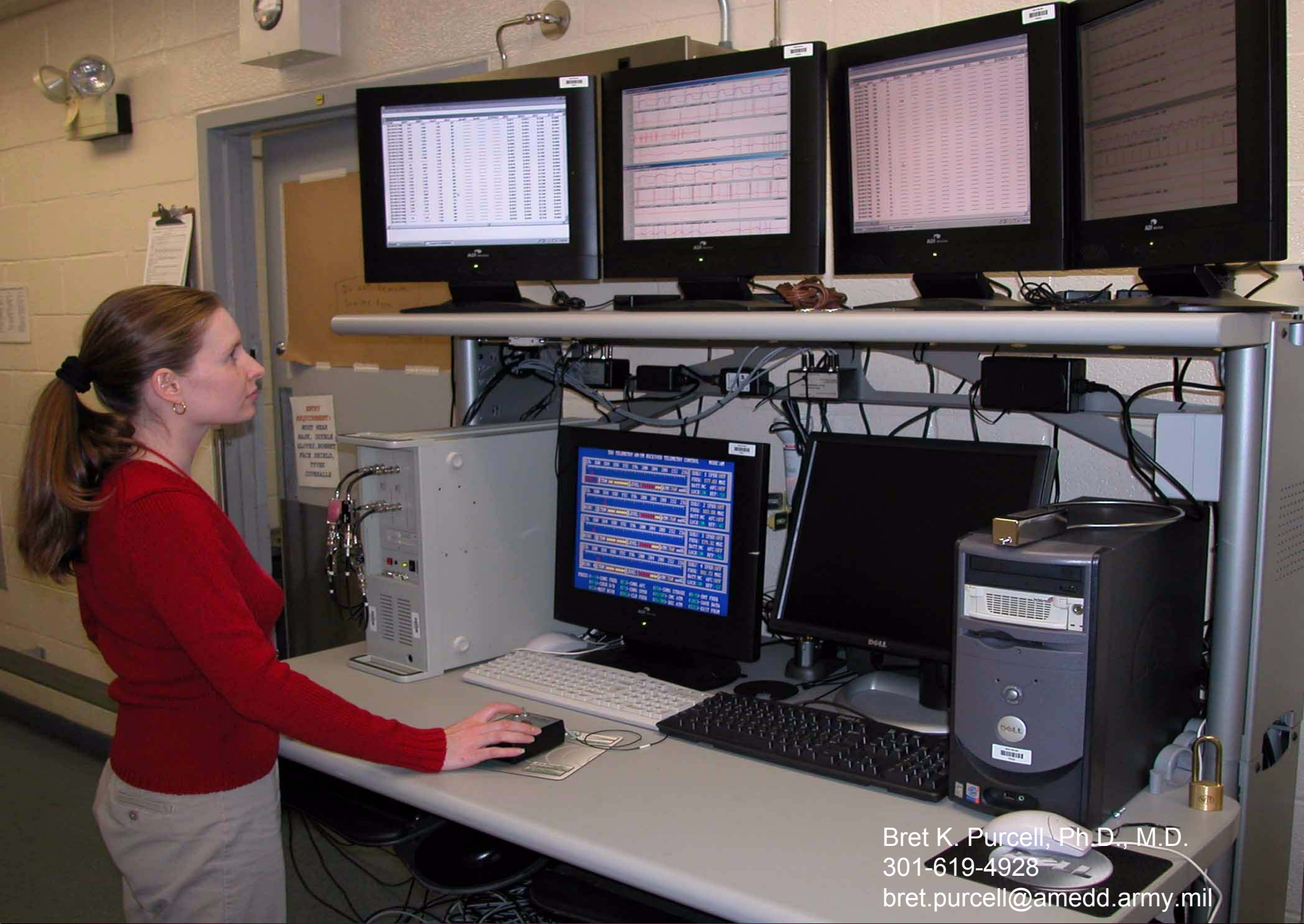


1 10:21 AM



# Advantages of ITS Telemetry

- ◇ Monitors multiple parameter continuously, 24 hrs / 7 days, every second of the day
- ◇ Standard Battery Life – For NHP: 15 – 24 months continuous use, on-off
- ◇ Improved Signal Range, Fidelity, Bandwidth/Freq Response and Signal to Noise Ratio
- ◇ Multiple frequencies allowing for pair or group housing
- ◇ Multiple sensor capability to reduce number of animals and experiments required

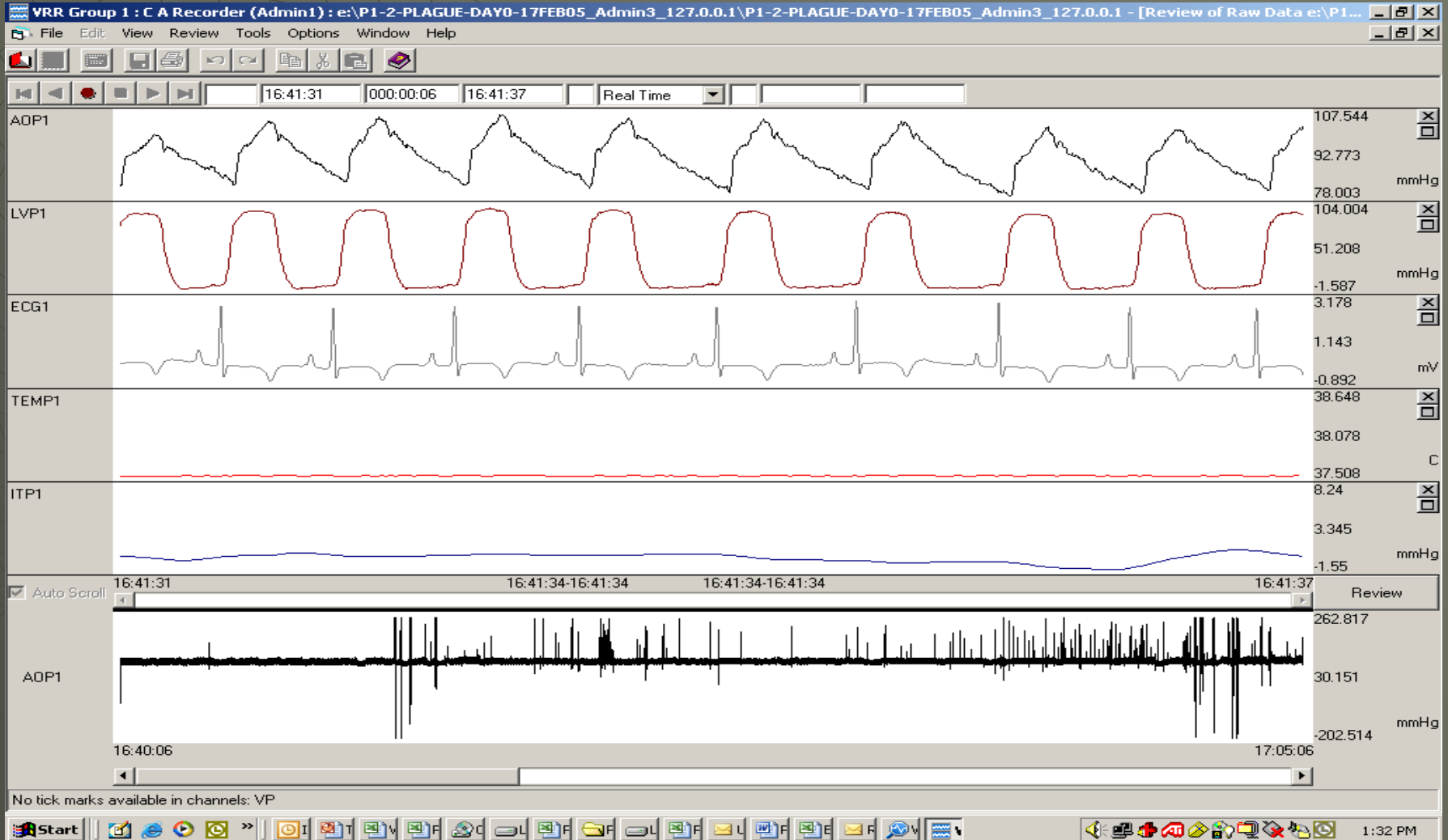


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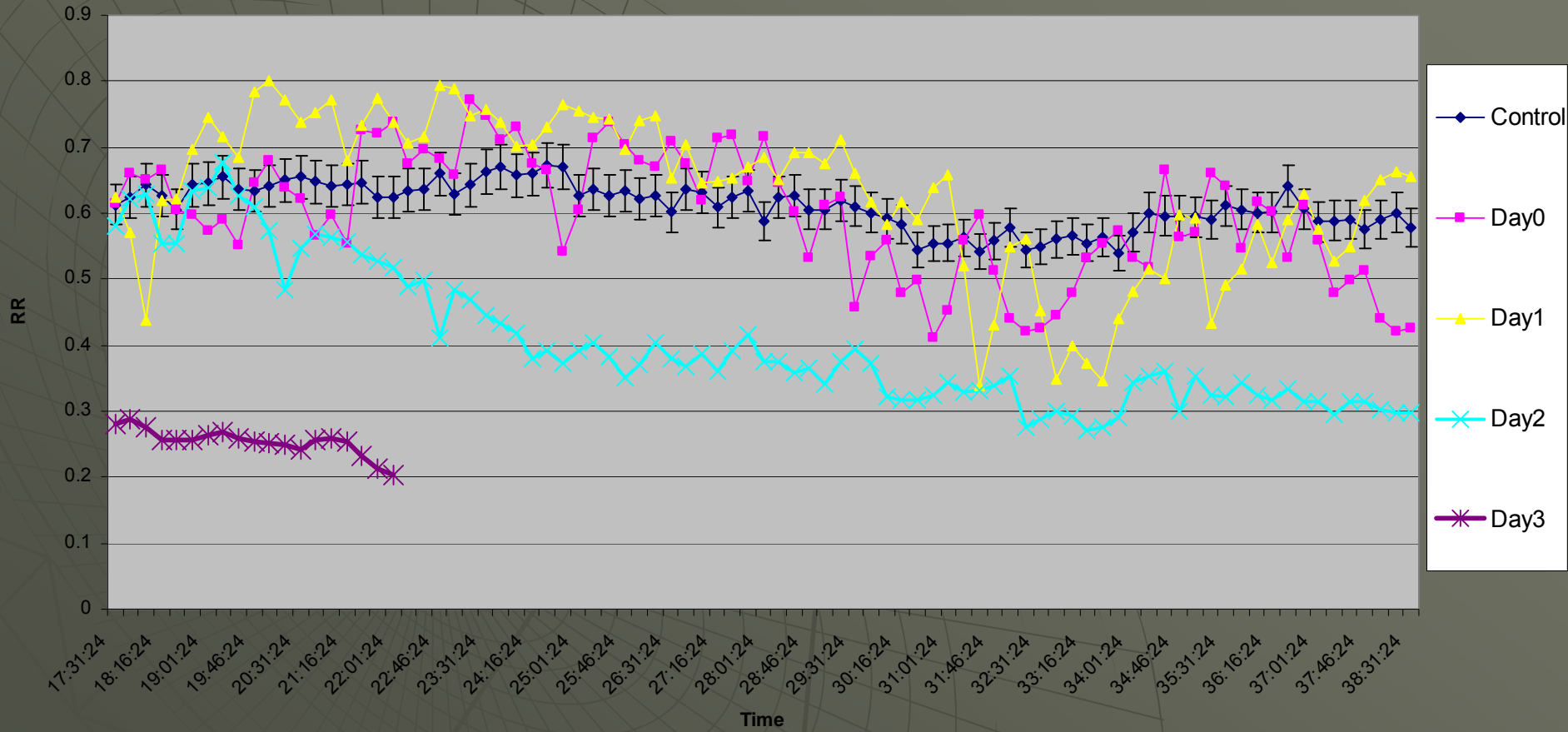


# Plague Challenge Day 0



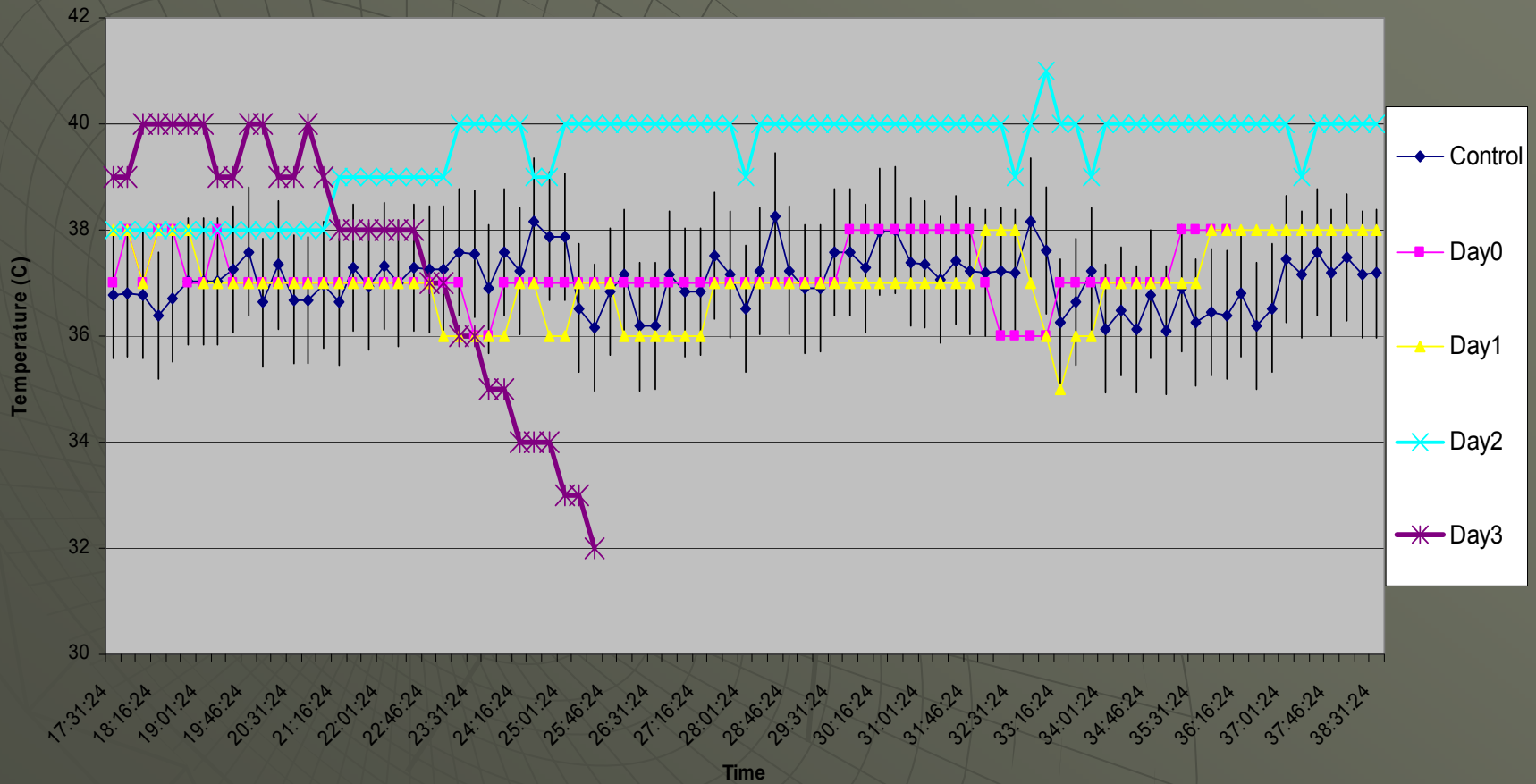


# Respiratory Rate





# Temperature



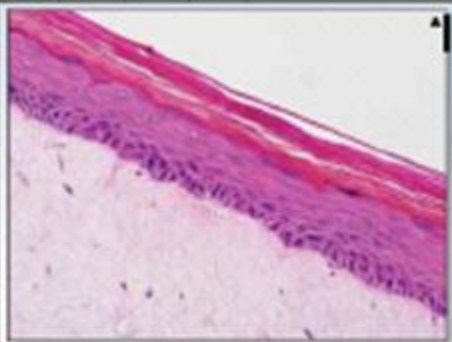


# Evaluation of Cytokine Activity of Three Human Tissue Constructs for In Vitro Sulfur Mustard Research

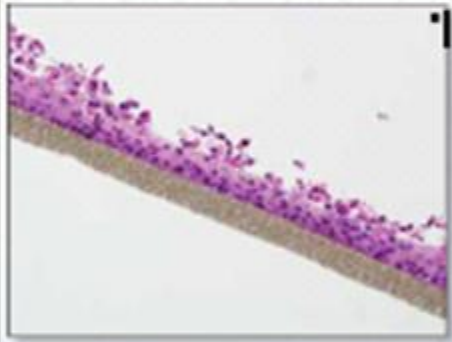
Adele Miller, Offie Clark, Clinton Cario, Eric Nealley, Robert Kan and William Smith

Research Division, US Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Maryland 21010-5400

EpiDerm™



EpiAirway™



Corneal Epithelial Cell Model™

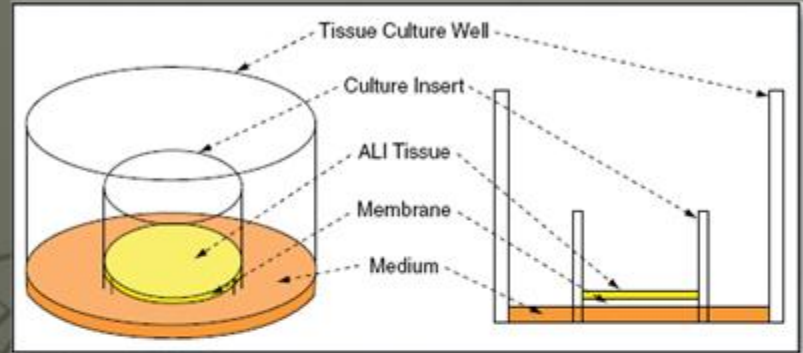
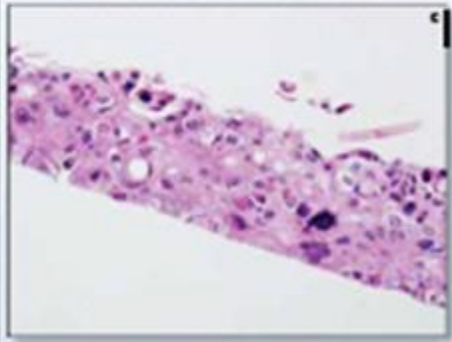


TABLE 1. Models to Use to Quantify Inflammatory Cytokines

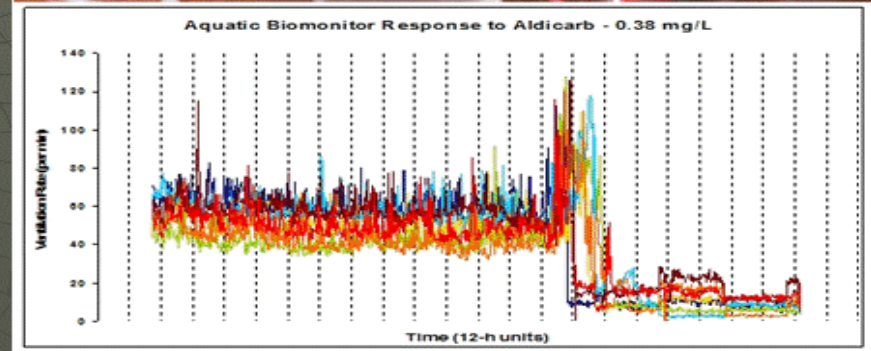
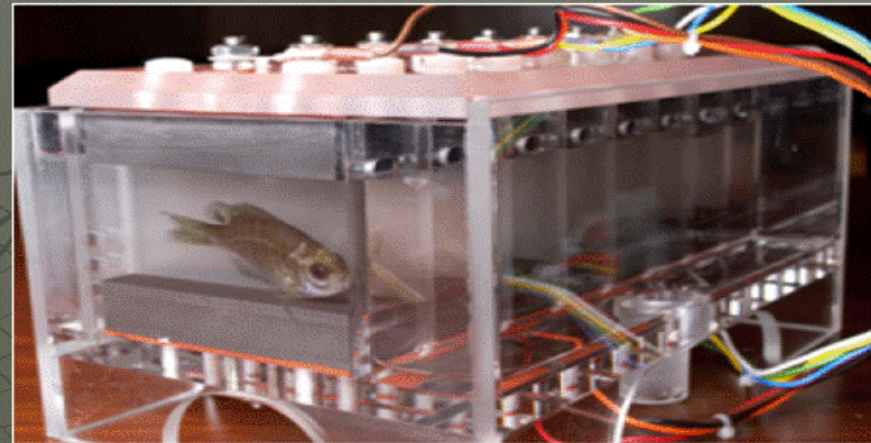
	EpiDerm FT	Corneal	EpiAirway
GM-CSF	+	+	NC
IL-1 $\beta$	NC	NC	NC
IL-6	-	+	+
IL-8	+	+	NC
TNF- $\alpha$	NC	+	NC

+ represents an up regulation of cytokine activity  
 - represents a down regulation of cytokine activity  
 NC represents that either no change of cytokine activity occurred or that none was detectable  
 Biosource 10 Plex kits contain 2 set of antibodies- "Inflammatory" and "TH/TH2."  
 Cytokines in the "TH1/TH2" category were either not detected or showed no change and thus are not portrayed on this table



# USACEHR Environmental Sentinel Monitor

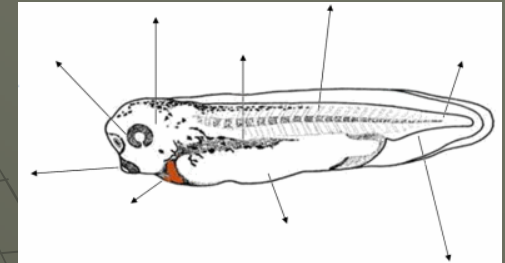
- ◆ 1<sup>st</sup> generation:  
Bluegills
- ◆ 2<sup>nd</sup> generation  
Immortalized frog  
melanocytes and  
primary bovine lung  
microvascular  
endothelial cells





# US EPA-Funded Endocrine Disruptor Studies (USACEHR)

- ◇ Early *X. tropicalis* tadpoles exposed to a range of concentrations of chemicals and allowed to develop to early adulthood
- ◇ Sex ratios, growth, reproductive and other developmental parameters studied
- ◇ Perchlorate to be tested





# FETAX

- ◇ 96-hour whole-embryo developmental toxicity test
- ◇ Uses early-stage embryos of the South African clawed frog (*Xenopus laevis*) to measure the effects of chemicals on mortality, malformation, and growth inhibition
- ◇ Proposed as a screening assay to identify potential human teratogens and developmental toxicants.



# FETAX Findings:

- ◇ Widespread interest/need for alternative approaches to detect potential for developmental toxicity
- ◇ FETAX is not sufficiently optimized or validated for regulatory studies
- ◇ Problems exist with result variability
- ◇ Expand the number of endpoints examine
- ◇ Further develop the application, validation and utilization criteria
- ◇ Use *Xenopus tropicalis* should be explored





# FETAX

- ◇ Due to extreme assay variability and difficulty of use, USACEHR does not have plans to further develop this assay



# Botulinum Toxin Testing

- ◇ Evaluates the serospecificity of botulinum neurotoxins to be used in pivotal animal efficacy studies
- ◇ Study results will be used to support a Biologics License Application (BLA) application to the FDA
- ◇ Mice are injected IP with botulinum toxin in a 96 hour test
- ◇ No early endpoint used
- ◇ Possible candidate study for early endpoint or alternative in vitro test



# USDA CVB Early Endpoint

Moribund animals exhibiting clinical signs consistent with the expected disease pathogenesis that are unable to rise or move under their own power may be humanely euthanized and considered as deaths as outlined in 9 CFR 117.4.

When implementing humane endpoints, equal treatment must be given to both vaccinated and control animals; ideally, observers should be blinded to treatment group assignment. Criteria should be as objective as possible, to minimize differences in individual interpretation.



Army  
Veterinarians  
make a  
difference!



**THE STRENGTH TO HEAL**  
and the satisfaction of helping those who  
help our Soldiers.

**Capt. Lenora Dickson, a field services veterinarian at Ft. Lewis, Wash.,** is proud to care for our government service animals. She also enjoys diverse duties such as inspecting our Soldiers' food supply, performing research to eradicate diseases and traveling for humanitarian missions. Capt. Dickson also plans to gain new skills through a specialized residency, master's degree or Ph.D. program. There's strong. Then there's Army Strong. Talk to a member of the U.S. Army or U.S. Army Reserve Health Care Team today; call XXX-XXX-XXXX or visit [healthcare.goarmy.com/info/XXXX](http://healthcare.goarmy.com/info/XXXX).



**ARMY STRONG.**

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1. With regard to the current portfolio of agency activities and their applicability to the development and validation of alternative test methods that will further reduce, refine, and replace animal use for regulatory safety testing:
  - a. Are there any gaps in the portfolio?
  - b. Are there areas that should be strengthened?
2. How might NICEATM and ICCVAM strengthen their leadership role in identifying and promoting R&D activities among the 15 Federal agencies that will produce alternative methods applicable to regulatory testing needs?