TEXAS BIOMEDICAL RESEARCH INSTITUTE

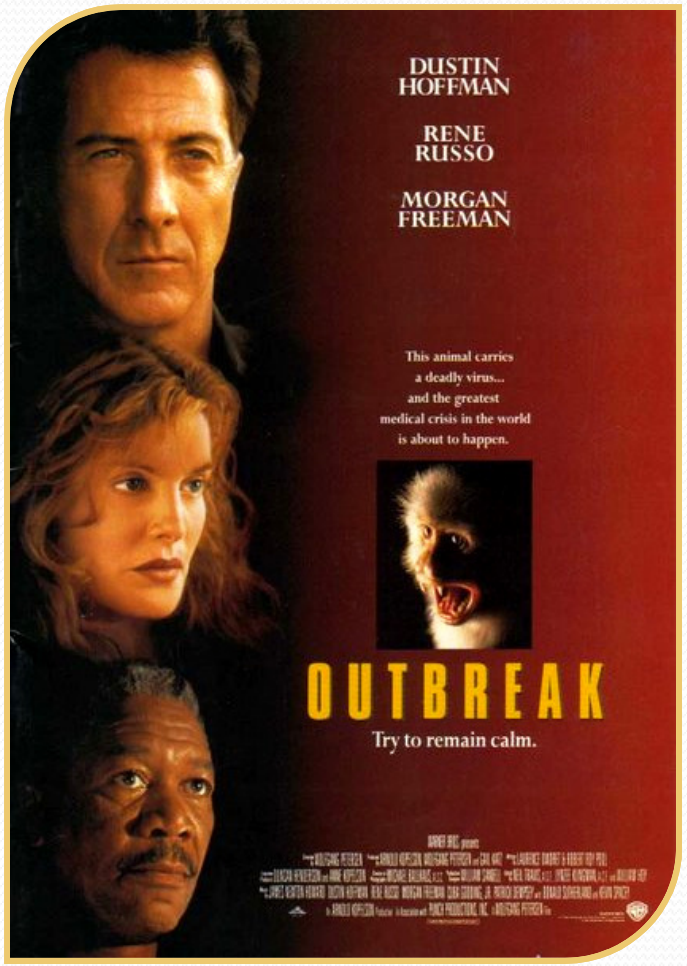
Enhancing lives through discovery.

Vaccine Development at Animal Biosafety Level Four: Standards and Challenges

Jean L. Patterson, Ph.D.
Chair, Department of Virology and Immunology

Texas Biomed BSL4 PIs:
Ricardo Carrion, Jr., Ph.D.
Robert Davey, Ph.D.
Anthony Griffiths, Ph.D.
Andrew Hayhurst, Ph.D.
Luis Giavedoni, Ph.D.

Select Agent Research

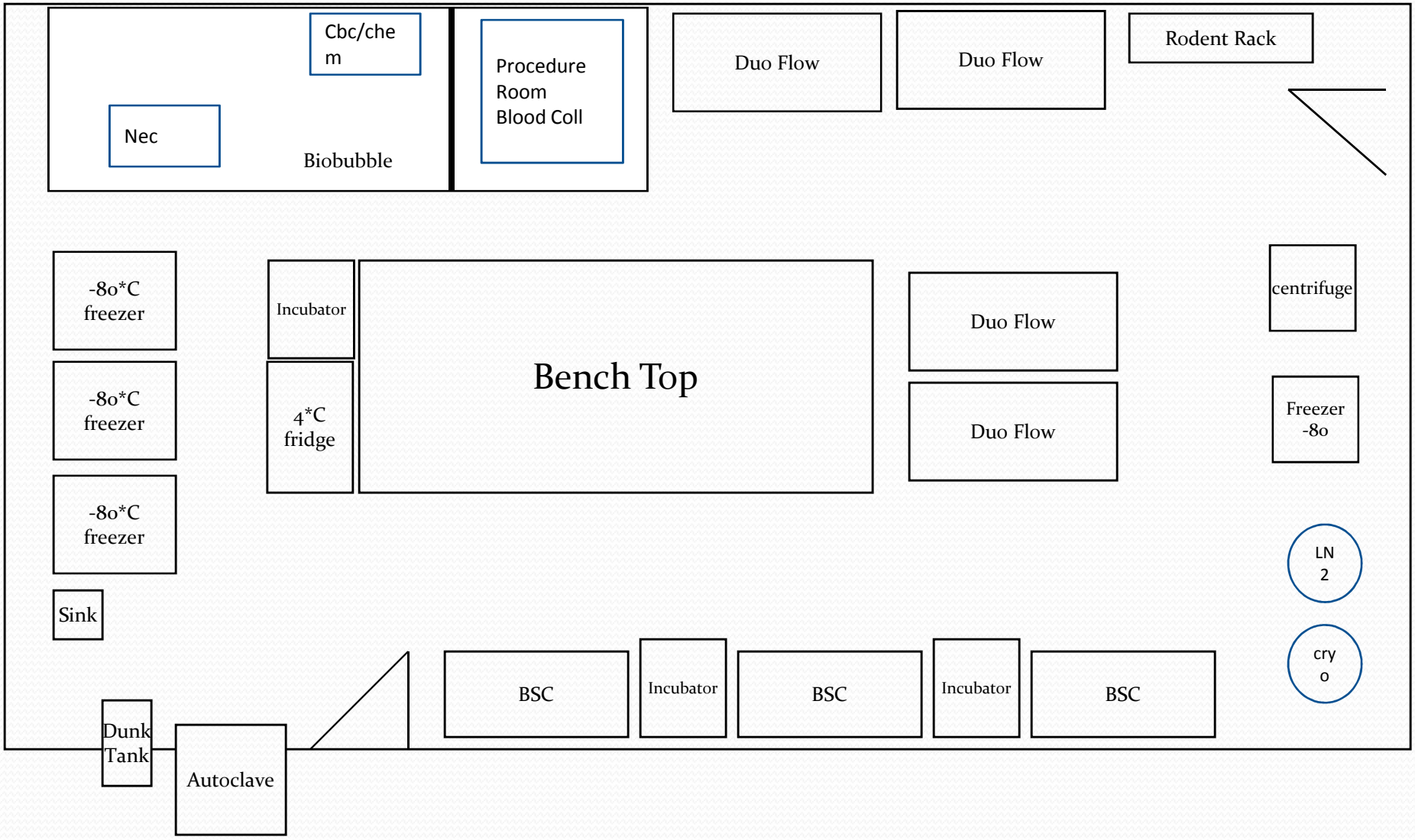




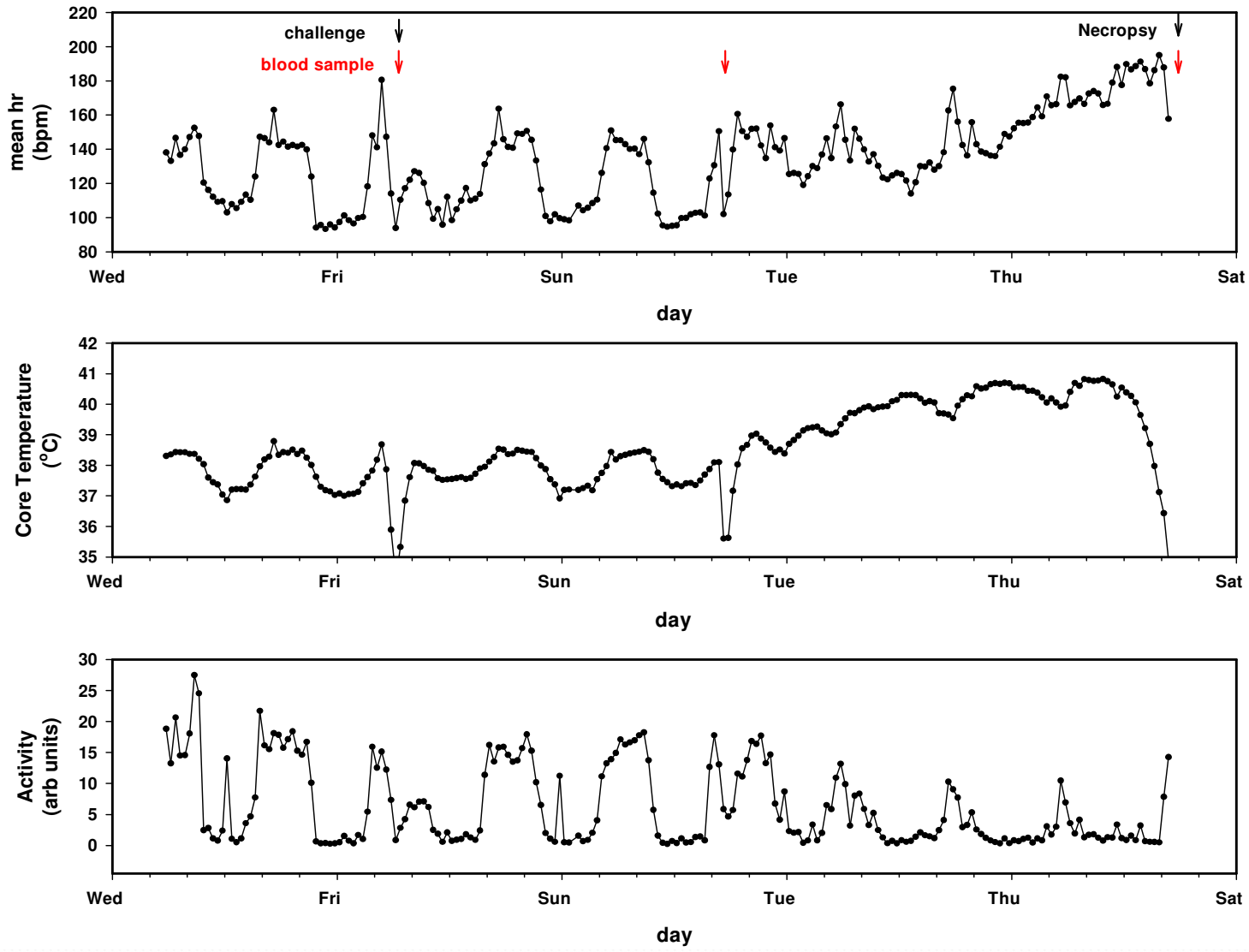


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Texas Biomed ABSL-4 Layout



TELEMETRY IN FILOVIRUS INFECTED NHPS



Biobubble: Procedure Area

- Macaques and Marmosets
- Inoculation NHPs
- Blood Collection
- Blood Analysis
- Necropsy
- Air Line drops
- Clear vinyl allows for appropriate lighting
- Certified annually



Duo Flow: NHP Housing

- Macaques=4
- Marmosets=6
- Consistent environmental conditions
- Light levels not affected by duo flow, additional lighting in ceiling of unit



Duo Flow: NHP Housing

- Easy access to NHPs
- Sedation of NHPs via squeeze mechanism
- Additional PPE used
- Air changes and light levels Compatible with "the guide"



Duo Flow: NHP Housing

- Sedated NHPs
- PPE worn
- Easy access to NHPs
- Permits dry husbandry

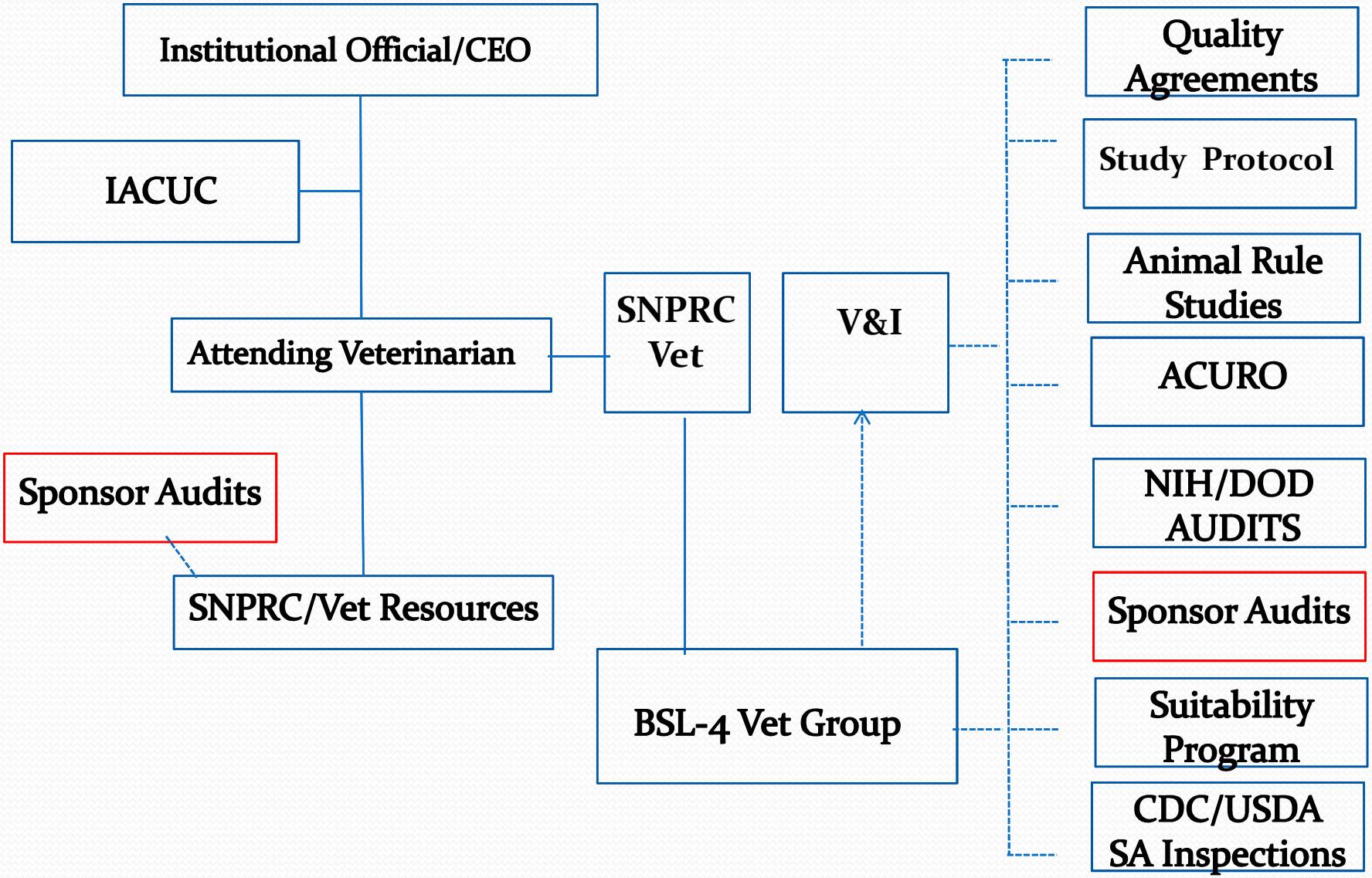


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Duo Flow and Dry Husbandry

- Dry Husbandry easily performed
- Minimized potential for aerosols




Institutional Official/CEO
IACUC
Attending Veterinarian
Sponsor Audits
SNPRC/Vet Resources
SNPRC Vet
V&I
BSL-4 Vet Group
Quality Agreements
Study Protocol
Animal Rule Studies
ACURO
NIH/DOD AUDITS
Sponsor Audits
Suitability Program
CDC/USDA SA Inspections

ABSL4 MAF DAILY OBSERVATIONS REPORT. IACUC #:

Start date (move in ABSL4 date): **Principal Investigator:**

Texas Biomed Animal ID: **MAF**	Observation Da	10.17.2013	10.17.2013	10.17.2013	10.17.2013	
Study Plan:	Project Day	Day Am	Day Am	Day Pm	Day Pm	
Time of Observations: (Am/Pm)		hrs	hrs	hrs	hrs	
Observer's initials:						
Scribe's initials						
Baseline Body weight: (Date of weight: Day 0):		kgs	kgs	kgs	kgs	
Baseline Rectal temperature: (Date of temperature: Day 0) :		^{0}F	^{0}F	^{0}F	^{0}F	
Today's Body weight:		kgs	kgs	kgs	kgs	
Today's Rectal Temperature:		^{0}F	^{0}F	^{0}F	^{0}F	
CATEGORIES (scoring criteria)					********CLINICAL SCORES*******	
Weight loss#. **0**: no change from baseline. **1**: 10-19%↓. **2**: > 20%↓						
Temperature#. **0**: no change from baseline. **1**: >2^{0}F. **2**: >3^{0}F. **3**: >5^{0}F.						
RESPONSIVENESS 0 = Alert, responsive, normal activity, free of disease signs or exhibits only resolved/resolving disease signs **1** = Slightly diminished general activity, subdued but responds normally to external stimuli; **2** = Withdrawn, may have head down, fetal posture, hunched, reduced response to external stimuli; **8** = Prostrate but able to rise if stimulated, moderate to dramatically reduced response to external stimuli; **15** = Persistently prostrate, severely or completely unresponsive, may have signs of respiratory distress						
Hair coat. **0**: = normal appearance. **1**: = rough hair coat						
Respiration. **0**: normal breathing. **3**: labored, Dyspnea. **8**: Agonal.						
Petechia* **0**: none. **1**: mild, >40%. **2**: moderate, 40-80%. **3**: severe, >80%						
Bleeding. **0**: none. **1**: at bleeding site. **2**: other then bleeding site						
Nasal discharge. **0**: not present. **1**: present						
Feed eaten. **0**: 100% -25% **1**: <25%						
Food enrichment. **0**: 100% - 25% **1**: <25%						
Stool: **0**: normal. **1**: no stool present. **2**: diarrhea/decreased volume						
Fluid Intake. **0**: drinking. **1**: reduced fluid intake. **2**: not drinking.						
Dehydration [1]. **0**: Normal, **1**:>2sec						
Total Clinical Score [2] **=**						

Total Clinical Score is determined by adding up all Clinical scores. Clinical scores are reported to responsible veterinarian daily. If clinical score is >8, the animal is reported to study veterinarian for evaluation. If total score is >15, animal is considered "terminally ill" and should be euthanized. Exceptions require consultation and approval by study veterinarian. Additional Euthanasia criteria: Humanely euthanize the animals as soon as any of the following: 1) Prostrate but able to rise if stimulated, moderate to dramatically reduced response to external stimuli with greater than 5 degree change from baseline or 2) Prostrate but able to rise if stimulated, moderate to dramatically reduced response to external stimuli and if any two of the following are true: ALT >200; ALP>1100; GGT>170; BUN>30; ALB<3.0. the veterinarian will approve all euthanasia

Daily Husbandry and Project Procedures. (No Clinical Score)					
Cage cleaning: **1** = pan cleaned **3** = wire bottom					
Water (H20): **1** = water added to bottle. **2** = fresh bottle & water.					
Fresh Feed: **1** = biscuits added to feeder. **2** = fresh feeder and biscuits.					
Other: **1** = sedated. **2** = project bled. **3** = found dead. **4** = sacrificed.					
Mechanism of Observation. (No Clinical Score)					
Personnel should record the following: **Direct Viewing code (1), viewing via camera code (2)** **Limited camera view code (3) or (4); depending on specific observation. See ABSL-4 observations.**					

All corrections on this form must be made in accordance with SOP 205.

HF= Hold Feed PF = Pull Feed **Scale Serial Number: 0042527-68D**

Initial Tech QC Review

Euthanasia

- If total score is >15, animal is considered "terminally ill" and should be euthanized. Exceptions require consultation and approval by study veterinarian.
- Additional Euthanasia criteria: Humanely euthanize the animals as soon as any of the following:
  - 1) Prostrate but able to rise if stimulated, moderate to dramatically reduced response to external stimuli with greater than 5 degree change from baseline or
  - 2) Prostrate but able to rise if stimulated, moderate to dramatically reduced response to external stimuli and if any two of the following are true: ALT >200; ALP>1100; GGT>170; the veterinarian will approve all euthanasia

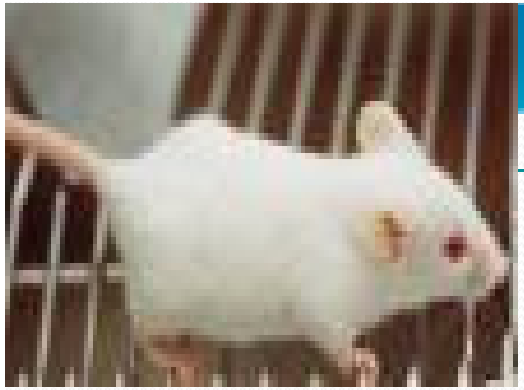
Observation Frequency

Animals will be observed twice daily when animals score less than 4, if animals score 4 to 8 animals will be observed three times a day.

Observations will be increased to 4 times a day, 6 hours apart if any of the following is true:

- An animal scores 8 or greater during clinical observation
- Analgesic treatment is initiated

Once an animal is euthanized due to morbidity, 4 times daily observations as described above will continue for three consecutive days for the remaining animals in the challenge cohort or until all surviving animals score 0.



The Animal Rule



- "New Drug and Biological Drug Products: Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible"
  - 21 CFR 601, Subpart H (Biologics)
  - 21 CFR 314, Subpart I (Drugs)
- It is NOT a simplified or expedited development process
- Does not apply if approval can be based on efficacy standards elsewhere in FDA regulations

The Animal Rule (cont.)

- Can be applied to human drugs/biologicals – not devices/diagnostics
- To reduce or prevent serious or life threatening conditions caused by exposure to lethal or permanently disabling toxic chemical, biological, radiological, or nuclear substances
- Use of animal efficacy data scientifically appropriate.
- Animal Rule does NOT address human safety

The Animal Rule (cont.) Requirements

- There is a reasonably well-understood pathophysiological **mechanism of the toxicity** of the substance and its prevention or substantial reduction by the product
- The effect is demonstrated in **more than one animal species** expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans

The Animal Rule (cont.) Requirements

- The animal study endpoint is clearly related to the desired benefit in humans, generally the **enhancement of survival or prevention of major morbidity**
- The data or information on the pharmacokinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows **selection of an effective dose in humans**

Ensuring Data Quality and Integrity in Animal Studies

- A good guideline – GLP (21 CFR Part 58)
  - GLP principles are among examples of quality management systems that will ensure the quality and integrity of data that is the basis for regulatory decision making
  - FDA recognizes that not all aspects of GLP will be possible for all studies – discuss with your review division
- Data quality and integrity are critical in animal efficacy studies as these data are the "surrogates" for the human efficacy studies
  - Natural history studies – model defining studies submitted for Qualification
- Adequate and well-controlled efficacy studies – substantial evidence of effectiveness
- Efficacy and PK/PD studies – define the human dose/regimen

Animal Rule (cont.)

- Still need human clinical data
  - PK/immunogenicity data
  - Safety in population(s) representative of use
- Approval subject to post-marketing studies
- May impose restrictions on use
- Please work closely with FDA on planning animal studies before starting them
- *Potential limitations*
  - Where there is no valid animal model of disease
  - How to predictably bridge animal data to humans
  - Confidence may be an issue, even in valid models

Risk/Benefit for MCMs

- Risk/benefit differs and FDA assesses for each product & potential use
  - Treatment: For otherwise untreatable serious illness, reasonable to tolerate significant risk & some uncertainty
  - Prophylaxis: If given to well individuals before event or, post-event, to individuals who may not be at risk, balance shifts
- All such products
  - Need transparent, balanced and effective risk communication; may be challenging in emergencies

Thanks!

- CBER's CT page: http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ProductSecurity/ucm110311.htm
- Manufacturer's assistance (CBER):
  - Phone – (301) 827-2000
  - http://www.fda.gov/cber/manufacturer.htm
- C. Kelley – (301) 827-0636
  - Cynthia.Kelley@fda.hhs.gov
- R. Roberts (CDER)– (301) 796-2210
  - Rosemary.Roberts@fda.hhs.gov