Vaccine Development at Animal Biosafety Level Four: Standards and Challenges

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Select Agent Research

OUTBREAK
Try to remain calm.
TELEMETRY IN FILOVIRUS INFECTED NHPS

**Mean HR (bpm):**
- Wed: 80
- Thu: 100
- Fri: 120
- Sun: 140
- Tue: 160
- Sat: 180
- Mon: 200

**Core Temperature (°C):**
- Wed: 35
- Thu: 36
- Fri: 37
- Sat: 38
- Sun: 39
- Mon: 40
- Tue: 41

**Activity (arb units):**
- Wed: 5
- Thu: 10
- Fri: 15
- Sat: 20

**Events:**
- Challenge
- Blood sample
- Necropsy
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
Duo Flow and Dry Husbandry

- Dry Husbandry easily performed
- Minimized potential for aerosols
ABS4 MAF DAILY OBSERVATIONS REPORT. IACUC #:

Start date (move in ABS4 date):  
Texas Blinded Animal ID:  
MAF  

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<tbody>
<tr>
<td>Time of Observations: (Am/Pm)</td>
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<tr>
<td>Observer’s Initials:</td>
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<td>Scribe’s Initials</td>
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Baseline Body Weight: (Date of weight: Day 0) | kgs | kgs | kgs | kgs |
Baseline Rectal Temperature: (Date of temperature: Day 0) |  |  |  |  |

Today’s Body Weight: | kgs | kgs | kgs | kgs |
Today’s Rectal Temperature: |  |  |  |  |

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**CATEGORIES (scoring criteria)**

**Weight loss**: 0 = no change from baseline. 1 = 10-19%, 2 = >20%

**Temperature**: 0 = no change from baseline. 1 = <90°F, 2 = 90°-93°F, 3 = >93°F

**RESPONSIVENESS** 0 = Alert, responsive, normal activity, free of disease signs or exhibit only reversible disease signs 1 = Slightly diminished general activity, subdued but responds normally to external stimuli; 2 = Withdrawn, may have head down, hunched, reduced response to external stimuli; 3 = Prostrate but able to raise if stimulated; moderate to dramatically reduced response to external stimuli; 4 = Persistently prostrate, severely or completely unresponsive, may have signs of respiratory distress

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**Hair coat**: 0 = normal appearance. 1 = rough, matted coat

**Respiration**: 0 = Normal breathing. 1 = labored, Dyspnoea. 2 = Agonal

**Pelvis**: 0 = none. 1 = mild >40%. 2 = moderate 40-80%. 3 = severe >80%

**Bleeding** 0 = none. 1 = at bleeding site. 2 = other than bleeding site

**Nasal discharge**: 0 = not present. 1 = present

**Feed intake**: 0 = 100% - 25% 1 = >25%

**Food enrichment**: 0 = normal. 1 = no food present. 2 = changed/reduced volume

**Stool**: 0 = normal. 1 = semi-formed stool. 2 = diarrhoea/decreased volume

**Fluid intake**: 0 = drinking. 1 = reduced fluid intake. 2 = not drinking

**Dehydration**: 0 = Normal. 1 = ?

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**Total Clinical Score**: 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: Humane euthanize the animals as soon as any of the following: 1) Prostrate but able to raise if stimulated, moderate to dramatically reduced response to external stimuli with greater than 5 degree change from baseline or 2) Prostrate but able to raise if stimulated, moderate to dramatically reduced response to external stimuli and if any two of the following are true: AL1 >200; ALP >1100; GGT >170; BUN >60; ALB >0.9. the veterinarian will approve all euthanized

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**Daily Husbandry and Project Procedures. (No Clinical Score)**

**Cage cleaning**: 1 = poor, clean 2 = good, clean

**Water (H2O)**: 1 = water added to bottle. 2 = fresh water & bottle

**Fresh Feed**: 1 = licks added to feeder. 2 = Fresh feeder and licks

**Other**: 1 = water 2 = project task. 3 = feed 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 ABS4 observations.

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

ID#: Head Feed IF= Null Feed Scale Serial Number: 0042527-65D 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:**

- **Manufacturer’s assistance (CBER):**
  - Phone – (301) 827-2000
  - [http://www.fda.gov/cber/manufacturer.htm](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