

FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research

*Antiviral Drugs Advisory Committee (AVDAC) Meeting*  
FDA White Oak Campus, Building 31, The Great Room (Rm. 1503)  
White Oak Conference Center, Silver Spring, Maryland  
December 14 - 15, 2011

**Questions to the Committee**

1. What animal model or models would be most appropriate for extrapolating the effects of a drug to anticipated efficacy in treatment of human smallpox? In your discussion, please address the following:

- a) Which aspects of human smallpox are most important to replicate in an animal model?
- b) Which model(s) do you think might best predict treatment response in human smallpox and why?
- c) How important is an animal model of variola virus infection as a component of a smallpox development program?
- d) If an adequate variola model is not possible, or if scientific limitations of the available variola model preclude definitive efficacy assessments, what data from what combination of other animal models using surrogate orthopoxviruses (e.g. non-human primate studies with monkeypox virus, rabbit studies with rabbitpox virus, mouse studies with ectromelia) could be used as evidence along with, or potentially instead of, animal studies using variola virus?
- e) *Based on the discussions that transpired, the following question was added during the meeting:* If feasible, do we need to have the same animal models for each antiviral drug being developed for treatment of established human smallpox illness?

2. With respect to a potential treatment indication for smallpox, please discuss the following study design elements for animal models:

- a) The route of viral challenge, inoculum size and viral strain/isolate for use in animal models that would most closely parallel human smallpox.
- b) Selection of endpoints: include discussion of secondary endpoints such as clinical and laboratory markers that might complement or support the assessment of mortality as a primary endpoint.
- c) Clinical manifestations to be used for initiation of treatment.
- d) Timing of treatment initiation relative to onset of clinical manifestations, to best represent likely timing of recognition of established illness and institution of treatment in humans if a smallpox outbreak were to occur.
- e) Duration of treatment and post-treatment follow-up to document and confirm resolution of infection and illness.
- f) Virological resistance assessments.

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3. If limited human data can feasibly and ethically be obtained from clinical trials of other naturally occurring orthopoxviruses, or if other human data (e.g. randomized controlled safety and dose-response data from non-orthopoxvirus diseases for drugs with appropriate spectrum of activity) are available, what potential role might such data provide as supportive evidence?