Food and Drug Administration
Center for Drug Evaluation and Research

Summary Minutes of the Antiviral Drugs Advisory Committee
December 14 – 15, 2011

Location: FDA White Oak Campus, Building 31, the Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland.

Topic: The committee discussed pathways for the development of drugs intended to treat variola virus infection (smallpox) in the event of an outbreak, including the use of animal models of other orthopoxviruses (the group of viruses that includes smallpox) as potential evidence of efficacy.

These summary minutes for the December 14 - 15, 2011 Meeting of the Antiviral Drugs Advisory Committee of the Food and Drug Administration were approved on __2/29/2012____

I certify that I attended the December 14 - 15, 2011 meeting of the Antiviral Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

_____**/Signed/**_____
Paul T. Tran, R.Ph
(Designated Federal Officer, AVDAC)

_____**/Signed/**_____
Victoria Cargill, M.D., M.S.C.E.
(Acting Chair, AVDAC)

Summary Minutes of the Antiviral Drugs Advisory Committee Meeting
December 14 - 15, 2011

The following is the final report of the Antiviral Drugs Advisory Committee meeting held on December 14 - 15, 2011. A verbatim transcript will be available in approximately six weeks, sent to the Division of Antiviral Products and posted on the Food and Drug Administration (FDA) website at:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/ucm247236.htm

All external requests for the meeting transcript should be submitted to the CDER Freedom of Information Office.

The Antiviral Drugs Advisory Committee of the FDA Center for Drug Evaluation and Research, met on December 14 - 15, 2011 at the FDA White Oak Campus, Building 31, the Great Room (Rm. 1503), White Oak Conference Center, Silver Spring, Maryland. Prior to the meeting, the members and temporary voting members were provided the background materials from the FDA, Chimerix, Inc., and SIGA Technologies, Inc. The meeting was called to order by Victoria Cargill, M.D., M.S.C.E. (Acting Chair), and the conflict of interest statement was read into the record by Paul Tran, R.Ph. (Designated Federal Officer). There were approximately 200 people in attendance on day 1 and 150 people on day 2. There was one Open Public Hearing speaker.

Issue: The committee discussed pathways for the development of drugs intended to treat variola virus infection (smallpox) in the event of an outbreak, including the use of animal models of other orthopoxviruses (the group of viruses that includes smallpox) as potential evidence of efficacy.

Attendance:
Antiviral Drugs Advisory Committee Members Present (Voting):
Elizabeth Connick, M.D.; Jeffrey S. Glenn, M.D., Ph.D.; Yoshihiko Murata, M.D., Ph.D.; Doris B. Strader, M.D.; Russell B. Van Dyke, M.D.

Antiviral Drugs Advisory Committee Members Not Present (Voting):
Susan Ellenberg, Ph.D.; Curt Hagedorn, M.D.; Thomas Giordano, M.D., M.P.H.; Barbara McGovern, M.D.

Temporary Members (Voting):
John Bennett, M.D.; Rudolf "Skip" Bohm, Jr., D.V.M., DACLAM; Victoria A. Cargill, M.D., M.S.C.E. (*Acting Chair*); Matthew B. Goetz, M.D.; Donald A. Henderson, M.D., M.P.H.; Rick C. Lyons, M.D., Ph.D.; Harold S. Margolis, M.D.; Alan J. Magill, M.D., FACP, FIDSA; Daniel Raymond (*Acting Consumer Representative*); Barth L. Reller, M.D.

Acting Industry Representative to the Committee (Non-voting)
Joseph Camardo, M.D.

Guest Speakers (Non-voting):
R. Mark Buller, Ph.D.; Richard W. Moyer, Ph.D.; Professor Geoffrey L. Smith, FRS

Speakers (Non-voting):
Mark D. Challberg, Ph.D.; Inger K. Damon M.D., Ph.D., FIDSA; Ali S. Khan M.D., M.P.H.; Gerald R. Kovacs, Ph.D.; Eric M. Mucker, M.S.

FDA Participants (Non-voting):
Edward Cox, M.D., M.P.H.; Debra Birnkrant, M.D.; Rosemary Roberts, M.D.; Mary Singer, M.D., Ph.D.; Kirk Chan-Tack, M.D.

Designated Federal Officer: Paul Tran, R.Ph

Open Public Hearing Speaker: Kieren P. Knapp, D.O., FACOFP

The agenda proceeded as follows:

Day 1: Wednesday, December 14, 2011

Call to Order and Introduction of Committee	**Victoria A. Cargill, M.D., M.S.C.E.** Acting Chair, AVDAC
Conflict of Interest Statement	**Paul T. Tran, R.Ph** Designated Federal Officer, AVDAC
FDA PRESENTATION	
Welcome and Introduction: Approaches to Antiviral Drug Development for Treatment of Human Smallpox	**Debra Birnkrant, M.D.** Director, Division of Antiviral Products (DAVP) Office of Antimicrobial Products (OAP) Office of New Drugs (OND), CDER, FDA Health and Human Services (HHS)
Historical Perspective on Smallpox	**Barbara Styrt, M.D., M.P.H.** DAVP, OAP, OND, CDER, FDA, HHS
SPEAKER PRESENTATION	
Smallpox Antivirals for Treatment: Public Health Perspective and Considerations	**Ali S. Khan M.D., M.P.H.** Assistant Surgeon General (retired), USPHS Director, Office of Public Health Preparedness and Response (OPHPR), CDC, HHS
HHS Smallpox Antivirals Program	**Gerald R. Kovacs, Ph.D.**

	Director Division of Chemical, Biological, Nuclear and Radiological **(**CBRN) Countermeasures Biomedical Advanced Research and Development Authority (BARDA) Assistant Secretary for Preparedness and Response (ASPR), HHS

FDA PRESENTATION

The Animal Rule	**Rosemary Roberts, M.D.** Director Office of Counterterrorism & Emergency Coordination, CDER, FDA, HHS

GUEST SPEAKER PRESENTATION

Orthopoxviruses: Properties, Phylogeny and Spread	**Professor Geoffrey L. Smith, FRS** Chairman World Health Organization (WHO) Advisory Committee for Variola Virus Research Wellcome Trust Principal Research Fellow Head, Department of Pathology University of Cambridge, United Kingdom

Clarifying Questions for Drs. Styrt, Khan, Kovacs, Roberts, and Smith

BREAK

GUEST SPEAKER PRESENTATIONS

Mousepox (Ectromelia Virus) Challenge Model	**R. Mark Buller, Ph.D.** Professor Department of Molecular Microbiology and Immunology Saint Louis University School of Medicine
The Rabbitpox Virus/Rabbit Model of Poxvirus Infection Elucidates Novel Aspects of Host-Virus Interaction	**Richard W. Moyer, Ph.D.** Professor Department of Molecular Genetics and Microbiology University of Florida College of Medicine

SPEAKER PRESENTATIONS

Susceptibility of Marmosets (*Callithrix jacchus*) to Monkeypox Virus	**Eric M. Mucker, M.S. (Ph.D. Candidate)** U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) Virology Division, Viral Therapeutics Branch

SPEAKER PRESENTATIONS *(cont.)*

Non-Human Primate (NHP) Monkeypox Model Development	**Mark D. Challberg, Ph.D.** Program Officer; Virology Branch Division of Microbiology and Infectious Diseases National Institute of Allergy and Infectious Diseases National Institutes of Health (NIH), HHS
Animal Models of Smallpox NHP Challenge/Variola Virus	**Inger K. Damon, M.D., Ph.D., FIDSA** CAPT, USPHS Branch Chief, Poxvirus and Rabies Division of High Consequence Pathogens and Pathology (DHCPP) National Center for Emerging and Zoonotic Infectious Diseases, CDC, HHS

Clarifying Questions from Committee for Drs. Buller, Moyer, Challberg, Damon, and Mr. Mucker

LUNCH

INDUSTRY PRESENTATIONS	**Chimerix, Inc.**
Developing CMX001 for the Treatment of Smallpox Under the "Animal Rule"	**Randall Lanier, Ph.D.** Senior Director, Virology Chimerix, Inc.

Clarifying Questions from Committee to Chimerix, Inc.

INDUSTRY PRESENTATIONS	**SIGA Technologies, Inc.**
Towards Approval of a Smallpox Antiviral Drug: Challenges and Progress	**Dennis Hruby, Ph.D.** Chief Scientific Officer SIGA Technologies, Inc.

Clarifying Questions from the Committee to SIGA Technologies, Inc.

BREAK

FDA PRESENTATION

Challenges and Study Design Issues in Smallpox Drug Development	**Kirk Chan-Tack, M.D.** Medical Officer DAVP, OAP, OND, CDER, FDA, HHS

Clarifying Questions from the Committee to FDA

Open Public Hearing

ADJOURNMENT

Day 2: Thursday, December 15, 2011

Call to Order and Introduction of Committee	**Victoria A. Cargill, M.D., M.S.C.E.** Acting Chair, AVDAC
Conflict of Interest Statement	**Paul T. Tran, R.Ph.** Designated Federal Officer, AVDAC
Charge to the Committee	**Debra Birnkrant, M.D.** Director DAVP, OAP, OND, CDER, FDA, HHS

Questions to the Committee/Committee Discussion

BREAK

Questions to the Committee/Committee Discussion

ADJOURNMENT

Questions to the Advisory 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? **(Discussion)**

Committee Discussion: *The committee strongly recommended targeting several aspects of human smallpox, specifically replication of the virus. The committee also stressed that cell targeting, host-response interaction, and host-pathogen interaction should be explored. The committee expressed some concerns regarding the routes of inoculation and the need to differentiate between the effects observed during the early and late stages of infection. However, the committee acknowledged that some of the animal models seemed to address those concerns. Regarding the animal models, some members remarked that these types of models are the best that we have and that we need to look at the complex interplay between the host and virus, and the characteristics of the overall viral strains. The committee recommended that the Agency be flexible and evaluate more than one animal model since one animal model would not be sufficient to address all the concerns regarding the different agents for treatment. Several members stressed the need to have a better understanding of the different stages of the clinical manifestation of the disease so that the treating physician on the front lines of a smallpox outbreak will be much more informed of how to treat infected individuals. Please see the transcript for details of the committee discussion.*

b) Which model(s) do you think might best predict treatment response in human smallpox and why? **(Discussion)**

Committee Discussion: *There was a general consensus that there are three leading models: the ectromelia (mouse) model, the rabbit model, and the monkey model. Although the rabbit model may be the most relevant, it may be more appropriate to consider triangulation across all three models. Some members expressed concerns regarding the cost and feasibility of such models and that cost will need to be taken into account. Additionally, it was noted that there is still a need for better models to look at viral inoculation via aerosolization as well as late-stage (using IV viral inoculation. Please see the transcript for details of the committee discussion.*

c) How important is an animal model of variola virus infection as a component of a smallpox development program? **(Discussion)**

Committee Discussion: *The committee noted that an animal model of variola virus infection is limited in several ways: 1) only two sites have variola virus since it is very strictly controlled and requires certain type of laboratory practices; and 2) some sites have difficulty meeting the Good Laboratory Practice (GLP) standards. More importantly, trying to have an animal model for variola is extremely challenging because a great deal of manipulation has to be performed in order to infect the one animal available for study. Please see the transcript for details of the committee discussion.*

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? **(Discussion)**

Committee Discussion: *The committee agreed that this question has been addressed by the committee throughout the discussions of questions #1a, #1b and #1c. The committee noted that further discussion was needed regarding endpoints, route of viral inoculation, and timing of treatment initiation. Please see the transcript for details of the committee discussion.*

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? **(Discussion)**

Committee Discussion: *The committee suggested that, given the varying attributes and limitations of the three models, it would be most appropriate to evaluate all three models discussed. This would allow for the use of a wider range of data and a stronger analysis of the effect of antivirals on host-response and host-interaction. Please see the transcript for details of the committee discussion.*

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. **(Discussion)**

Committee Discussion: *Some committee members recommended that the study design focus on the route of viral challenge and pushed for those using mortality as a primary endpoint where there are no questions regarding the impact of the therapeutic challenge. There was some discussion as to whether mortality in the placebo group for models should be 100% or not, but there was no general consensus reached by the committee on this issue. There were some discussions about whether the challenge route should necessarily reflect the route of exposure (respiratory) in actual human smallpox infection. The committee again raised the issue of cost as it may not be feasible to conduct studies if it is very expensive. The committee also expressed that there should be a therapeutic window in the model, i.e. there should be sufficient time between inoculation and acute disease to treat the animal. Please see the transcript for details of the committee discussion.*

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. **(Discussion)**

Committee Discussion: *The committee noted that some endpoints relevant to human infection (such as complete blood count (CBC) and metabolic or hepatic profile) may not be useful in translating results of animal studies to analyses of human infection. The committee highlighted the measure of viral load to the drug as a potential secondary endpoint. Please see the transcript for details of the committee discussion.*

c) Clinical manifestations to be used for initiation of treatment. **(Discussion)**

Committee Discussion: *The committee stressed the difficulty in making the correct diagnosis as individuals often present with a wide range of clinical manifestations (pre-exposure, post-exposure, and varying degrees of fever, viremia, and rash). However, the committee noted that it would be helpful to know the general effect on the animal's well-being and to know the point at which the animal or human is beyond saving. They further noted that treatments will be used in a wide range of settings and there will be a need for a good risk mitigation strategy. Please see the transcript for details of the committee discussion.*

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. **(Discussion)**

Committee Discussion: *The committee indicated that the issue of timing of treatment was discussed during the discussion of question #2c above. Several members expressed that the timing will depend on the type of outbreak (a single small outbreak versus a mass outbreak across multiple locations) as this would affect the timing and the scale of the treatment initiated. It was also mentioned that there is a limited amount of investigational agents for treatment in an outbreak and this would affect the timing of initiation. Please see the transcript for details of the committee discussion.*

e) Duration of treatment and post-treatment follow-up to document and confirm resolution of infection and illness. **(Discussion)**

Committee Discussion: *The committee indicated that residual DNA might be a helpful indicator for duration of treatment. One committee member suggested that it would also be helpful to evaluate these investigational agents in the context of administration in conjunction with the smallpox vaccines. The committee noted that data presented by SIGA Technologies, Inc. indicated that ST-246 did not interfere with immune response when, when co-administered with vaccines, such as Dryvax in mice and monkeys. Chimerix, Inc. noted that there was minimal interference with immune response when CMX001 was co-administered with live smallpox vaccine. There was some discussion as to whether duration of treatment could be determined by using immune markers, i.e. once immune response to vaccine has been elicited, the drug could be stopped. The committee also discussed which people should be considered as the best candidates for drug treatment and/or vaccination, taking the various clinical circumstances into consideration; however the committee expressed uncertainty as there is not enough data/information to fully provide the FDA with a recommendation at this time. Please see the transcript for details of the committee discussion.*

f) Virological resistance assessments. **(Discussion)**

Committee Discussion: *The committee expressed the need to assess not only the resistance but the resistance in relation to the dosage and timing of drug treatment. Additionally, the following should be evaluated: mechanism of action involved with the drugs in use, how these drugs bind and work, and the development of drug resistance. The committee expressed that we need to know more about the genetic barrier to resistance for both drugs. The committee recommended looking at immunocompromised animals in these models, as there would likely be more viral shedding which would allow for a better sense of how these animals respond and the degree of drug resistance. Additionally, there was some discussion as to whether both drugs should be evaluated in combination in case of resistance. The committee expressed some concerns regarding primary resistance as well as resistance as the result of drug therapy. It was noted that how well non-variola virus resistance correlates with variola virus resistance should be determined. Please see the transcript for details of the committee discussion.*

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? **(Discussion)**

Committee Discussion: *The committee indicated that it would be important to obtain additional data about the safety of these antiviral drugs but expressed concern over the difficult challenge in extrapolating results from non-orthopoxvirus human data to variola. It was noted that it would be helpful for the Agency to know if there are protocols for smallpox treatment already in place in the event of an outbreak, and also protocols for individuals who*

develop vaccinia infections as complication of vaccination. It may also be important to gather information from those who declined to participate in these protocols to ensure some data from them can be obtained so that we don't have any missed opportunity to learn about the pathogenesis/ natural history of smallpox from these patients. In addition, it would be helpful to have pharmacodynamic and pharmacokinetic data derived especially from individuals who have conditions such as hepatic or renal insufficiency, which may be seen in cases of severe smallpox infection. It was noted that high-quality data may be difficult to obtain depending on the number of outbreak sites, the remoteness of the sites, and the logistical difficulty of response collection. Please see the transcript for details of the committee discussion.

The meeting was adjourned at approximately 5:05 p.m. on day 1 and 11:25 a.m. on day 2.