

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208627Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 069019

MEETING PRELIMINARY COMMENTS

SIGA Technologies, Inc
Attention: Annie Frimm
Vice President, Regulatory, Clinical and Quality
4575 SW Research Way
Suite 110
Corvallis, OR 97333

Dear Ms. Frimm:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tecovirimat.

We also refer to your May 25, 2017, correspondence, received May 25, 2017, requesting a meeting to obtain the Agency's advice for the upcoming NDA planned for December 2017.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (240) 402-5708 or the main line at (301) 796-1500.

Sincerely,

{See appended electronic signature page}

Andrew Gentles, PharmD, BCPS AQ-ID
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: August 11, 2017, 1:00-2:30 PM
Meeting Location: White Oak Bldg 22, Rm 1311

Application Number: 069019
Product Name: tecovirimat
Indication: Treatment of [REDACTED] ^{(b) (4)} infection
Sponsor/Applicant Name: SIGA Technologies, Inc.

FDA ATTENDEES (tentative)

Edward M. Cox, MD, MPH, Director, Office of Antimicrobial Products (OAP)
John Farley, MD, MPH Deputy Director, OAP
Barbara Styrt, MD, MPH, Associate Director for Medical Countermeasures, OAP
Debra Birnkrant, MD, Director, Division of Antiviral Products (DAVP)
Jeffrey Murray, MD, MPH, Deputy Director, DAVP
Poonam Mishra, MD, Deputy Director for Safety, DAVP
Hanan Ghantous, PhD, DABT, Pharmacology/Toxicology Team Lead, DAVP
Laine Peyton Myers, PhD, Pharmacology/Toxicology Reviewer, DAVP
Adam Sherwat, MD, Clinical Team Lead, DAVP
Kirk Chan-Tack, MD, Clinical Reviewer, DAVP
Karen Winestock, Chief Project Management Staff, DAVP
Andrew Gentles, PharmD, BCPS AQ-ID, Regulatory Project Manager, DAVP
Julian O'Rear, PhD, Lead Clinical Virology, DAVP
Patrick Harrington, PhD, Clinical Virology Reviewer, DAVP
Stephen Miller, PhD, Chemistry, Manufacturing and Controls Lead,
Office of Pharmaceutical Quality (OPQ)
Yushi Feng, PhD, Product Quality Reviewer, OPQ
Shirley Seo, PhD, Clinical Pharmacology Team Lead, Office of Translational Sciences
(OTS), Office of Clinical Pharmacology (OCP), Division of Clinical Pharmacology IV (DCP IV)
Su-Young Choi, PhD, Clinical Pharmacology Reviewer, OTS/OCP/DCP IV
Thamban Valappil, PhD, Biometric Team Lead, OTS, Office of Biometrics, Division of
Biometrics IV (DBIV)
Wen Zeng, PhD, Biometrics Reviewer, DBIV
Rosemary Roberts, MD, Director, Counter-Terrorism and Emergency Coordination Staff
(CTECS)
Brad Leissa, MD, Deputy Director, CTECS

Susan McDermott, MD, Team Lead, CTECS
Gerald Poley, MD, Medical Officer, CTECS
Rebecca McKinnon, PharmD, Team Lead, Project Management Staff, CTECS
Andrea Gormley, PharmD, JD, Regulatory Project Manager, CTECS
Doris Auth, PharmD, Team Lead, Sr. Risk Management Analyst, OSE
Otto Townsend, PharmD, Team Lead, Division of Medication Error Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE)
Valerie Wilson, PharmD, DMEPA Reviewer, OSE

SPONSOR ATTENDEES

In Person

Dennis Hruby, Chief Scientific Officer
Paul Long, Director, Regulatory Affairs
Doug Grosenbach, Associate Director, Poxvirus Research
Ingrid Meara, Senior Director, Clinical
Annie Frimm, Vice President, Regulatory, Clinical and Quality

Via Teleconference

Kady Honeychurch, Associate Director, Project Management
Candace Lovejoy, Senior Project Manager
Lennie Pinkston, Director Regulatory Documentation
Lek Chinsangaram, Director Project Management
Biswajit Maiti, Director of Drug Metabolism and Pharmacokinetics
Tove' Bolken, Senior Vice President Operations

BARDA

In Person

Louise Latriano, Ph.D., Contractor to BARDA, Toxicology SME
Shar'Ron deDreu, Contractor to BARDA, Clinical Operations SME
Michael Merchlinsky, Ph.D., Nonclinical SME
Andrew Albright, Project Officer/Health Scientist

Via Teleconference

Chia-Wei Tsai; Branch Chief, Antiviral and Antitoxin Programs

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for August 11, 2017, 1:00-2:30 PM, FDA White Oak, Bldg 22, Room 1311 between SIGA Technologies, Inc and the Division of Antiviral Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original

questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face-to-face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

SIGA Technologies, Inc. (SIGA) is developing tecovirimat for the proposed indication of treatment of (b) (4) infection under the Animal Rule. On May 25, 2017, SIGA submitted a Pre-NDA meeting request to discuss REMS requirement, animal model justification, clinical dose justification, labeling, Track and Trace for SNS Resupply and granting of a Priority Review Voucher.

2.0 DISCUSSION

2.1. Category/Discipline A

Question 1: Based on the data available, can the Division now confirm that a REMS program will not be required?

FDA Response to Question 1: At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to conclusively determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks. We will make a final determination for the need for a REMS during the review of your application.

Question 2: Does the Division have any comments on this white paper? Does it provide adequate justification for the animal models studied? If not, what additional data would be needed, or what recommendations does the Division have?

FDA Response to Question 2: The white paper sufficiently addresses our earlier request that the NDA submission include a formal justification for the animal models studied. As previously discussed, the white paper should be submitted as a component of your initial NDA for our review.

Question 3: Does the Division have any comments on this white paper? Does it provide adequate justification for the selection of the final clinical dose of 600 mg BID to be included in the labeling documentation for TPOXX? If not, what additional data would be needed, or what recommendations does the Division have?

FDA Response to Question 3:

Please add the following information to the white paper.

- *Exposure (C_{max}, AUC, C_{min})- response (survival) analysis in both species*
- *PK comparison between infected NHPs and humans (including simulated median and 5th – 95th percentile)*

Also please submit the following study reports under NDA 208,627

- *Population pharmacokinetic analysis for NHPs and rabbits cited in the white paper*
- *NHP PK-survival analysis previously submitted under IND 69,019 (SN 158 and SN 172) and the datasets supporting the analysis*

Question 4: SIGA would greatly appreciate any comments the Division may have at this time on the draft labeling provided.

FDA Response to Question 4: Please note that the following comments related to the draft labeling are being provided as a courtesy and are subject to change based on our review of the complete NDA submission.

As a general comment, SIGA may benefit from reviewing recently approved, relevant prescribing information [e.g., ANTHIM (obiltoxaximab)] especially when drafting Sections 14 and 17 of the label. Also, SIGA may benefit from reviewing recently approved antiviral products' labels (e.g., drugs treating chronic hepatitis C infection) when drafting Sections 7 and 12 of the label.

Question 4(a): Will a Medication Guide or any other form of instructions for patients be required? If a Medication Guide is required, does the Agency have any comments on the one provided with the FPI?

FDA Response to Question 4 (a): Yes, patient labeling will be required for this product. Whether the required patient labeling will consist of a Patient Package Insert or Medication Guide will be an NDA review issue.

Question 4(b): Based on the data the Agency has received thus far, does the Division agree with SIGA's wording for the proposed indication of "TPOXX is indicated for treatment of (b) (4) infections?" This indication is in line with SIGA's orphan designation (b) (4)

FDA Response to Question 4 (b): Although it is premature for the Division to comment on the specifics of the proposed indication in labeling, our preliminary recommendation is that the indication be limited to the treatment of human smallpox disease caused by variola virus.

Question 4 (c): Does the Division agree that hypoglycemia should be included as a Warning and Precaution in Section 5?

FDA Response to Question 4 (c): Whether hypoglycemia should be included as a Warning in Section 5 will be an NDA review issue based on our independent review of the safety data.

Question 4(d): Is the presentation of drug interaction information in Section 7 – Drug Interactions acceptable to the Division?

FDA Response to Question 4 (d): The detailed contents of Section 7 are review issues. We have the following comments regarding the format of the proposed Section 7.

1. Please reformat section 7 using the following subheadings. You may add additional subheadings as necessary.

1. Potential for other drugs to affect TPOXX
2. Potential for TPOXX to affect other drugs
3. Established and potentially significant drug interactions. (you may include a table summarizing significant drug interactions and clinical recommendations).

2. Please re-format Table 4. Typically, a table in section 7 is organized by drug name, effect on concentrations, and clinical recommendations.

(b) (4)

Question 4 (e): Does the Division agree with SIGA's presentation of human pharmacokinetic information and dose selection justification in Section 12.3 – Pharmacokinetics?

FDA Response to Question 4 (e): The detailed contents of Section 12 are review issues. Overall, the format of 12.3 is acceptable except Fig 1 is not necessary. Statements on (b) (4) may be included as text under "Absorption". Also, in vivo DDI study results can be presented in a table format in 12.3. Refer to Guidance for Industry: Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format (published in 2016) for additional details.

Question 4 (f): In Section 12.4 Microbiology, the description of resistance does not provide specifics regarding resistant mutants or susceptibility. As TPOXX is a drug to be used in case of an act of bioterrorism, SIGA felt that this data could be used to facilitate the production of a mutant or resistant virus; therefore, this data was not included. We do inform the physician that resistance may develop in vivo and that they should consider this in the event that a patient does not respond to therapy or there is disease recrudescence after an initial period of responsiveness to tecovirimat. Does the Division agree with the type and amount of data provided regarding resistance?

FDA Response to Question 4 (f): While we recognize your concerns about publicizing tecovirimat resistance data, multiple resistance pathways for tecovirimat have already been published and therefore are publicly available (e.g., [Yang et al., 2005](#); [Lederman et al., 2012](#); [Duraffour et al., 2015](#)). Therefore, at this time we request that you include in this section of the draft label a summary of tecovirimat resistance findings from key cell culture and animal model studies. Ultimately the precise language in the label will be an NDA review issue.

Additional FDA Recommendations on Draft Prescribing Information

The statement in Section 1.2, (b) (4)

should be revised or expanded to convey the fact that multiple animal model studies indicate that tecovirimat may have reduced efficacy in the setting

of severe immune deficiency, at least when administered as monotherapy in the absence of any other intervention (e.g., immune reconstitution).

Statements throughout the draft prescribing information should specify "virus" when referring to the virus and not specifically the disease. For example, (b) (4)

*In Section 12.4, the proposed text, (b) (4),
(b) (4) is misleading and should be revised, as it is clear that tecovirimat has a relatively low resistance barrier, and certain single amino acid substitutions in the target p37 protein can confer very large reductions in tecovirimat antiviral activity. This section should note that tecovirimat has a low resistance barrier, and the emergence of drug resistant virus has been observed in cell culture and animal models of orthopoxvirus infection.*

Also in Section 12.4, the (b) (4) section should cross-reference Section 14.1.

Question 5:

You have indicated your intention to submit data from a human factors (HF) usability validation study post-original NDA approval. (b) (4)

See Additional Recommendations for information on conducting HF studies.

Question 6:

FDA Response to Question 6: We refer to your submission dated April 7, 2017. Additional comments will be provided in a subsequent communication.

Question 7: Does the Agency agree that, assuming the status of tecovirimat as an NCE does not change and that smallpox remains a significant material threat, SIGA would receive a PRV upon NDA approval? Is there a specific mechanism or form to complete

and include with our NDA filing to ensure that this occurs? When would SIGA receive notification of the issuance by FDA of a PRV?

FDA Response to Question 7: If the submitted New Drug Application (NDA) for tecovirimat meets all of the criteria for a material threat countermeasure application described in section 565A(a)(4) of the FD&C Act at the time that the NDA is approved, then it would be eligible for a material threat medical countermeasure Priority Review Voucher (MCM PRV):

- *A human drug application as defined in section 735(l) of the Food, Drug and Cosmetic (FD&C) Act:
 - *Intended for use to prevent or treat harm from a chemical, biological, radiological and nuclear (CBRN) agent identified as a material threat under section 319F-2(e)(2)(A)(ii) of the Public Health Service (PHS) Act; or*
 - *Intended to mitigate, prevent or treat harm from a condition that may result in adverse health consequences or death and may be caused by administering a drug or biological product against such agent**
- *Deemed by FDA to be eligible for priority review*
- *Approved by the FDA after the date of enactment of Cures (December 13, 2016) intended for use to prevent or treat a harm from a CBRN agent identified as a material threat under section 319F-2(e)(2)(A)(ii) of the PHS Act*
- *For a human drug, no active ingredient (including an ester or salt of the active ingredient) of which has been approved in any other application under section 505(b)(1) of the FD&C Act or section 351 of the PHS Act*

The original submission of the material threat MCM product application should include the sponsor's request describing how the application meets the eligibility criteria for a priority review voucher. There is no specific form available for this purpose. Please prominently identify the request as "Material Threat Medical Countermeasure Priority Review Voucher Request" and include or reference it in your cover letter.

If the application is approved, FDA will assess at the time of approval whether all the criteria for eligibility for a material threat MCM application under section 565A(a)(4) of the FD&C Act are met. If the NDA qualifies for receipt of a material threat MCM priority review voucher, the voucher is issued at the time of approval. Information related to the priority review voucher will be included in the approval letter for the material threat MCM application. This letter will include a priority review voucher identification number, which should be referred to when redeeming the voucher.

Additional Recommendations

General

1. *If the NDA application is approved, please confirm whether your product will be held exclusively in the SNS.*

Clinical Virology

2. *Please summarize available data that directly (i.e., cell culture or animal model) or indirectly (presence and amino acid identity of F13L/p37) address the potential activity of tecovirimat against human infectious poxviruses outside of the orthopoxvirus genus, such as molluscum contagiosum virus and parapoxviruses. Please include this summary in the completed NDA.*

Clinical

3. *Please provide narratives on all deaths, serious adverse events, or discontinuations due to adverse events in your clinical trials to date.*

Division of Medication Error Prevention and Analysis (DMEPA)

4. *Use your comprehensive use-related risk analysis to inform the design of a human factors validation study protocol for your product. Please note that a comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform (consider known problems for similar products), and the potential negative clinical consequences of use errors and task failures. Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable. We recommend you submit your study protocol to the IND for feedback from the Agency before commencing your study. Please note we will need 90 days to review and provide comments on the Human Factors (HF) validation study protocol. Plan your development program timeline accordingly.*

The following items will facilitate an efficient review of your HF study protocol:

- *A summary of preliminary analyses and evaluations, including formative studies;*
 - *Include in your summary a discussion of key findings and any changes made to your product or labeling, including how the findings were used to update the user interface and risk analysis*
- *An updated risk analysis for your product;*
- *Detailed HF validation study protocol to include the following elements:*
 - *Description of intended product users, uses, use environments, and training (if applicable) for commercial product*
 - *Graphical depiction and written description of product user interface*
 - *Summary of known use problems with previous models or similar products*
 - *User task selection, categorization (e.g., critical) and prioritization*
 - *Validation testing details*
 - *Objective(s)*
 - *Type of testing (simulated or actual use)*
 - *Test environment and conditions of use*
 - *Training provided to participants and rationale for how it corresponds to real-world training (if applicable)*

- *Distinct user groups broken out by number and type of test participants and rationale for how they represent the intended user populations*
- *Intend-to-market labels and labeling (including an editable word version of the IFU if an IFU is proposed) that will be tested in the HF validation study*
- *Five intend-to-market samples of product that will be tested in the HF validation study*

The requested information should be placed in eCTD section 5.3.5.4 – Other Study reports and related information.

Guidance on human factors procedures to follow can be found in:

Applying Human Factors and Usability Engineering to Medical Devices, available online at: <http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf>

Guidance on Safety Considerations for Product Design to Minimize Medication Errors and can be found online at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf>

Note that we recently published two draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development and can be found online at:

<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf>

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors and can be found online at:

<http://www.fda.gov/downloads/drugs/guidancecomplianceinformation/guidances/ucm349009.pdf>

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

Reference is made to the December 29, 2016, January 11, 2017 and February 6, 2017 communication that stated if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the

application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on PDUFA V and the Program is available at

<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER’s standard format for electronic regulatory submissions. As of **May 5, 2017**, the following submission types: **NDA**, **ANDA**, and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To

establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

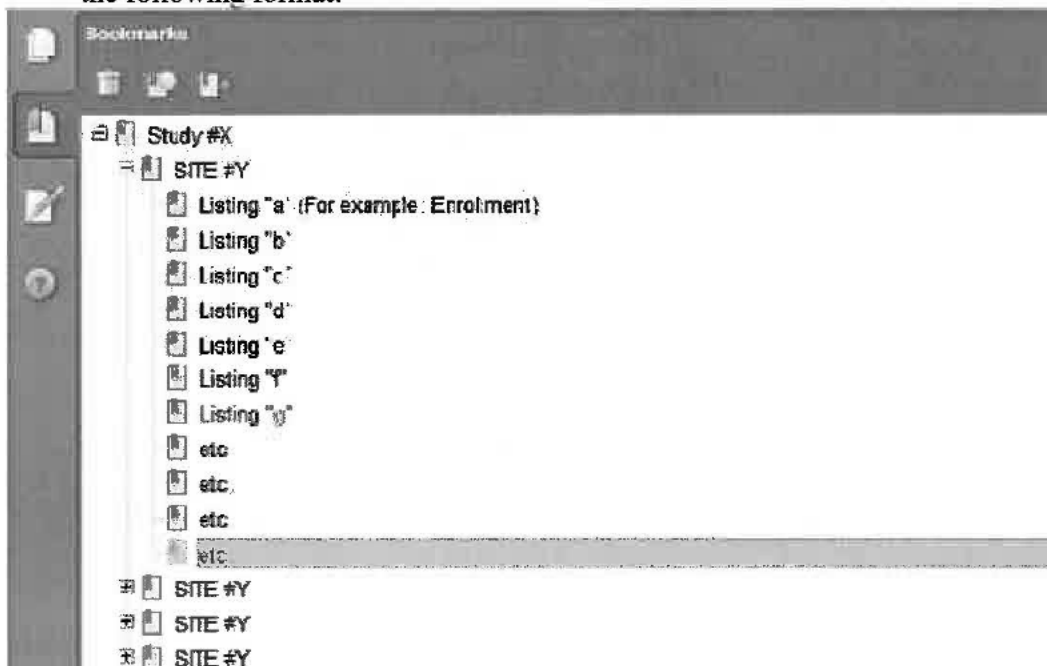
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:

- a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
 5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link

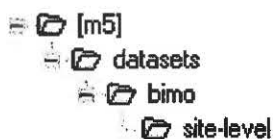
<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANDREW A GENTLES
07/27/2017



IND 69,019

MEETING PRELIMINARY COMMENTS

SIGA Technologies, Inc.
Attention: Annie Frimm
Vice President, Regulatory, Clinical and Quality
c/o 4575 SW Research Way
Suite 230
Corvallis, OR 97333

Dear Ms. Frimm:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tecovirimat.

We also refer to your December 15, 2016, correspondence, received December 19, 2016, requesting a meeting to discuss the content and format of your future NDA submission.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at 301-796-4876 or 301-796-1500.

Sincerely,

{See appended electronic signature page}

Sohail Mosaddegh, PharmD
Regulatory Project Manager
Division of Antiviral Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: February 6, 2017
Meeting Location: Teleconference

Application Number: 69,019
Product Name: Tecovirimat
Indication: Treatment of smallpox
Sponsor/Applicant Name: Siga Technologies Inc. (Siga)

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for February 6, 2017 between Siga and the Division of Antiviral Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

BACKGROUND

SIGA Technologies, Inc. (SIGA) is developing tecovirimat for post exposure treatment of (b) (4) under the Animal Rule.

DISCUSSION

Your questions from the December 19, 2016 meeting package are in **bolded** font followed by FDA response in *italicized* font.

Risk Evaluation and Mitigation Strategy

We have outlined below the benefit/risk ratio of tecovirimat based on statutory factors outlined in the Draft Guidance for Industry: FDA's Application of Statutory Factors in Determining When a REMS Is Necessary, September 2016. Based on our analysis, SIGA does not believe

that a Risk Evaluation and Mitigation Strategy (REMS) in the NDA would be required. We are seeking the Agency's concurrence on this matter.

FDAAA requires FDA to consider six factors in making a decision on the requirement for a REMS program. SIGA's comments are provided and address each of these six factors.

1. The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

The demonstration of the safety of tecovirimat includes human as well as animal data. Completed animal toxicology studies support the use of tecovirimat in humans.

Seven human clinical studies have been completed in healthy volunteer subjects, including five safety and PK studies and two taste masking palatability studies. Tecovirimat has been found to be safe and well tolerated in human safety and PK studies at single doses up to 2000 mg (fasted state), and multiple doses up to 800 mg QD for 21 days (fed state). In the completed clinical studies (excluding the palatability studies, in which tecovirimat was not ingested), approximately 523 healthy subjects have received at least 1 dose of tecovirimat and of those 523 approximately 435 subjects have received at least 14 days of once daily dosing. Of the 435 subjects receiving multiple days of dosing, approximately 334 subjects have received 600 mg BID for 14 days. No safety signals have been reported in these studies and there have been no drug-related serious adverse events.

The most commonly reported tecovirimat related AEs in the completed clinical studies were headache and nausea. Flatulence and fatigue have also been reported, but with less frequency.

In Study SIGA-246-002, one subject who received the highest tecovirimat dose (800 mg/day) for 16 days reported a severe headache which was deemed probably drug related (onset Day 15). With appropriate concomitant medication, this headache resolved. The occurrence of headache and nausea will be closely monitored in the six currently ongoing clinical studies (Expanded safety SIGA-246-008, DDI SIGA-246-015, Renal SIGA-246-012, Hepatic SIGA-246-013, QTc SIGA-246-010 and PK in Food/Liquid SIGA-246-018).

Data obtained during the recently completed enrollment of the SIGA-246-008 expanded safety trial at the clinical dose of 600 mg BID for 14 days supports the data derived from the previous 7 studies; i.e., the most commonly reported tecovirimat related AEs were headache and nausea (see Appendix A, Table 14.3.2.4.1). This study was conducted (completed) in approximately 420 subjects, with a ratio of 4 subjects on tecovirimat to 1 subject on placebo. There were no drug-related serious adverse events. The Data Safety Monitoring Board for this study provided the following comments at the final review meeting:

"The DSMB unanimously agreed: The study drug appears safe and well-tolerated. Any concerns about the potential risk of seizure were adequately addressed and defined by the design and outcome of the study. Data was discussed and it was concluded that no additional data analysis for safety events are indicated." (See Appendix B)

In the currently ongoing renal and hepatic studies, while data has not been audited, to date we have seen only the following drug-related AEs:

Renal Study SIGA-246-012:

Adverse Event ^a	Severity	Status
Nausea	Mild	Resolved
Nausea	Mild	Resolved
Increased Flatulence	Mild	Resolved
Constipation	Mild	Resolved
Asymptomatic Prolonged PR Interval	Mild	Resolved
Headache	Mild	Resolved
Lightheaded	Mild	Resolved
Nausea	Mild	Resolved

^aDoes not include any AEs that were determined to be not related or unlikely related.

Hepatic Study SIGA-246-013:

Adverse Event ^a	Severity	Status
Hypotension	Mild	Resolved

^aDoes not include any AEs that were determined to be not related or unlikely related.

Lastly in the currently ongoing QTc study, SIGA-246-010, (data not yet audited) all subjects have completed and we have seen the following tecovirimat/placebo-related AEs. The study remains blinded at this time.

Adverse Event ^a	Severity	Status
Headache	Mild	Resolved
Nausea	Mild	Resolved
Emesis	Moderate	Resolved

^aDoes not include any AEs that were determined to be not related or unlikely related.

In all studies either completed or ongoing, there have been no drug-related SAEs to date.

Of note, since smallpox was eradicated many years ago, sufficient clinical data is not available to confidently comment on the background incidence of adverse events in the population likely to use the drug. To the best of our knowledge, smallpox is not specific to any special populations, and anyone who is exposed to the virus will potentially be part of the disease population.

2. The expected benefit of the drug with respect to the disease or condition

Tecovirimat is being developed under the FDA “Animal Rule” and the demonstration of efficacy of tecovirimat followed the requirements of the Rule.

The expected benefit of tecovirimat with respect to human smallpox or other orthopox viral diseases is prevention of mortality and significant reduction in major morbidity. This expectation is based on results of numerous studies conducted both *in vitro* and *in vivo*. *In vitro* studies have demonstrated that tecovirimat is broadly active against, yet specific for all virus species within the orthopoxvirus genus. The antiviral activity is limited to the parent compound (major metabolites show no antiviral activity), which targets the p37 protein common to all orthopoxviruses, inhibiting the formation of egress-competent enveloped virions necessary for dissemination both *in vitro* and *in vivo*. *In vivo* studies were conducted in two animal models to support the clinical dose of 600 mg BID, models considered by FDA to be well-characterized and appropriate for evaluation of smallpox therapeutics in order to satisfy the requirements of the FDA Animal Rule. In non-human primate and rabbit efficacy studies, tecovirimat consistently provided 90-100% protection from mortality and prevented major morbidity, even when the drug was administered to symptomatic animals four days post infection.

3. The seriousness of the disease or condition that is to be treated with the drug

Smallpox is a serious, contagious and sometimes fatal infectious disease. It is believed to have originated thousands of years ago, and is one of the most devastating diseases known to humanity. The disease is associated with at least 30% mortality and high morbidity which would have a significant impact on the day-to-day functioning of those who contract this devastating disease. Smallpox is a significant bioterrorism threat facing the United States. In response to this danger, the US Government has made the development of a treatment for smallpox a priority for civilian defense.

Currently, there is no FDA approved drug for treatment of smallpox.

4. Whether the drug is a new molecular entity

FDA has defined the term “new molecular entity” as an active ingredient that contains no active moiety that has been previously approved by the Agency in an application submitted under Section 505 of the Act (in any application approved or deemed approved from 1938 to the present), or has been previously marketed as a drug in the United States. By this definition, tecovirimat would fall into the category of new molecular entity which would, if taken as the sole criterion for requiring a REMS program, suggest that a REMS should be completed.

5. The expected or actual duration of treatment with the drug

The anticipated dosage of tecovirimat is 600 mg capsule BID orally for 14 days and has not been associated with any serious adverse events at any time during dosing or after dosing. Furthermore, no specialized training is required to prevent the occurrence of an adverse event due to improper drug administration.

6. The estimated size of the population likely to use the drug

Tecovirimat has met the governmental requirements for inclusion in the Strategic National Stockpile (SNS). Through SIGA's contract with BARDA, the CDC SNS is being supplied with a total of 2 million tecovirimat treatment courses. At this time, it is unknown if any further purchases for the SNS will occur, [REDACTED] (b) (4)

Tecovirimat inhibits orthopox virus egress from infected cells and virus induced cytopathic effects. The compound does not affect cell proliferation and is specific to orthopoxviruses; therefore, we do not anticipate off-label use.

Question 1: Based on the above six points, SIGA believes a REMS in the NDA for tecovirimat will not be required. Does the Agency agree?

FDA response: It is premature for us to determine whether a REMS will be required for this NDA.

Advisory Committee Meeting

Over the past ~ twelve years, SIGA has worked very closely with the Agency on all aspects of the development of tecovirimat, and would appreciate the Agency's thoughts on the requirement for an Advisory Committee (AC) Meeting for the tecovirimat NDA review. [REDACTED] (b) (4)

Based on SIGA's review of the draft FDA Guidance for the Public and FDA Staff on Convening Advisory Committee Meetings (August 2008), SIGA has the following comments for the Agency to consider.

Tecovirimat is a first in class NCE and this is one of the criteria for taking a drug to Advisory Committee review.

Throughout the development of tecovirimat, multiple meetings and correspondence addressed the controversial issues surrounding the appropriate animal model to use since tecovirimat is being developed under the Animal Rule. This was resolved by the FDA Smallpox Advisory Committee Meeting held in December 2011. All final animal efficacy studies have been submitted to IND 69,019, FDA has audited the CROs conducting these studies and the studies do demonstrate the drug is "reasonably likely" to provide benefit. As per FDA correspondence of 11 October 2016 (Ref. ID: 3997286) and confirmed via email (email S. Mossadegh to A. Frimm dated 19 October 2016), no further animal efficacy studies are required to support the upcoming NDA for post-exposure treatment of orthopox viruses.

All safety pharmacology and toxicological studies have been completed and submitted to the IND.

The selection of an appropriate dose for tecovirimat was also the subject of significant discussion between the Agency and SIGA, as it was based on multiple evaluations and pharmacokinetic

modeling by SIGA, and finally the Agency's own pharmacokinetic modeling. A dose was finally agreed upon (FDA correspondence 17 February 2016, Ref ID 3888193) and clinical studies were initiated in support of the NDA. The draft pharmacokinetic data from the expanded safety and PK study (SIGA-246-008) show drug exposure above the C_{min} and AUC of the NHP model at 10 mg/kg and C_{max} below the CNS NOAEL in dogs (as modeled by FDA). All clinical studies support safety only. The clinical study report for the expanded safety trial will be submitted to the IND at least 7 months prior to NDA filing, and clinical study reports for all other studies in special populations (renal and hepatic), DDI and QTc will be submitted at least 4 months prior to NDA filing. Pharmacokinetic data from the co-morbid and DDI studies will support dosing adjustments, if required, within the label. (b) (4)

The manufacture and control of tecovirimat has been documented and submitted to the IND and reviewed by the Agency, including 84 month stability data. Pre-approval inspections of our manufacturing sites have also been conducted by FDA. Tecovirimat is now stockpiled within the CDC SNS.

Question 2: Can the Agency provide its thoughts on whether an Advisory Committee Meeting will be convened for the tecovirimat NDA?

FDA response: The Agency appreciates that you have worked closely with us to follow the advice provided during the 2011 Antiviral Drugs Advisory Committee meeting on the development of drugs to treat variola virus infection, and to address the key tenets outlined in the Draft Guidance for Industry entitled Smallpox (Variola) Infection: Developing Drugs for Treatment or Prevention. Although the final determination will be an NDA review issue, it is likely that an additional Advisory Committee will be needed for the tecovirimat NDA for reasons including, but not limited to, the following: 1) tecovirimat is a first-in-class new molecular entity; 2) the Agency's intention to be fully transparent regarding the challenges of smallpox drug development under the Animal Rule and; 3) the public health importance of a potential regulatory decision on an antiviral for treatment of human smallpox.

Animal Model Data/Dose Justification Support

As you know, BARDA has done significant work to establish the appropriate rabbit model to support SIGA's conduct of rabbit efficacy studies. Please refer to BARDA PIND 118,305 SN: 0025, dated 14 JUL 2015 for a list of studies.

Question 3: How does the Agency wish to treat this data? Should SIGA cross-reference to BARDA's PIND 118,305 within our NDA?

FDA response: Yes, cross-referencing to PIND 118,305 should be sufficient.

Question 4: Does the Agency require a justification or discussion of the animal model (NHP and rabbit) selection in the NDA? If so, would this be included in 2.6.2 Pharmacology Written Summary or within the ISE in Module 5.3.5.3? Or, if a justification

is required, would a white paper submitted to the IND and referenced in Section 2.6.2 or the ISE be preferable?

FDA response: Yes, your NDA should include discussion and justification of the animal model (NHP and rabbit) selection. The Sponsor may use their own discretion as to the preferred location within the NDA and the approach to doing so (e.g., submitted white paper, etc.).

Question 5: SIGA proposes to include discussions concerning the animal efficacy data and human dose justification in Section 2.6.2 Pharmacology as well as in the summary of the ISE data in Section 2.7.3 Clinical Efficacy. Does the Agency agree with this proposal? If not, would the Agency share where these discussions should be included?

FDA response: Your approach related to the discussions concerning animal efficacy data seems reasonable. Please submit justification for the human dose in section 2.7.2 (Summary of Clinical Pharmacology Studies). Also, modeling and simulation reports utilizing pharmacokinetic data from more than one study (e.g., population pharmacokinetics or exposure-response analysis using animal data) and datasets used for the analysis should be submitted in 5.3.5.3.

Module 4 Study Reports

Question 6: SIGA has attached a comprehensive list of Module 4 sections/subsections and within those sections, a list of nonclinical study reports that SIGA will be including in the NDA (see Appendix C). Can the Agency please verify that the location of these reports is appropriate within Module 4? If the Agency would prefer some reports to be placed in other sections or subsections, can you please provide us with your preference?

FDA response: Module 4 appears appropriate for nonclinical study reports. For ease of review, please be sure to organize Module 4 so that the safety studies (toxicology, safety pharmacology, etc.) are easily differentiated/separated from the animal rule efficacy studies.

Furthermore, the Division prefers that during the rolling review, the completed safety studies (tox, safety pharm, etc) are submitted very early in the cycle into Module 4. This will greatly help with the review of the large number of studies in Module 4.

ISE Data Integration

Question 7: As SIGA will be integrating animal efficacy data within the ISE, SIGA plans to convert the animal efficacy study data for the six identified "pivotal" animal efficacy studies to CDISC. Is this acceptable to the Agency?

FDA response: Yes.

Emergency Use Data Collection

In the past, FDA had requested in various correspondences the preparation of a clinical protocol to collect data for emergency use. It is our understanding, that the CDC's current protocol in IND 116,039 will be used for any emergency use of tecovirimat prior to NDA approval. Once

approved, it will be SIGA's responsibility to collect data from any use of tecovirimat. (b) (4)

Based on this scenario, SIGA does not plan on submitting any of the above-mentioned correspondence within Section 1.17 Postmarketing Studies in the initial NDA submission.

Question 8: Are our assumptions correct and does the Agency agree with the plan for not including any correspondence or data in Section 1.17?

FDA response: Please submit written documentation confirming that the CDC's current protocol in IND 116,039 will be used for any emergency use of tecovirimat prior to NDA approval. After you provide this information, we can provide additional feedback regarding your proposal for pre-approval emergency use.

Please note that approval of a drug under the Animal Rule includes a requirement for postmarketing studies (e.g., field studies) to provide evaluation of safety and clinical benefit if circumstances arise in which a study would be feasible and ethical (i.e., in the event an emergency arises and the drug is used). A plan or approach to conducting such a study must be included with the NDA [see 21 CFR 314.610(b)(1)].

Question 9:

a. SIGA requests to submit Module 3 as a rolling NDA review in mid-2017. Will the Division accept Module 3 before the rest of the NDA?

FDA response: See response to Question 9b.

b. If the Division will accept Module 3, Quality, as a rolling submission, will Module 2.3, Quality Overall Summary, also be expected as part of this submission?

FDA response: Yes, we would accept a complete set of CMC information as a rolling submission. In addition to Module 3, that should also include the Quality Overall Summary in Module 2, proposed Prescribing Information and Container Labels, facility information / readiness for inspection, and Letters of Authorization for any Drug Master Files in Module 1.

Question 10: SIGA will be requesting priority review and is planning to include this within the cover letter accompanying the full NDA package to be submitted in late 2017. If the Division grants SIGA a rolling review of Module 3 should the request for priority review be noted in the cover letter for the Module 3 Rolling Review, or only included as part of the cover letter for the full NDA submission?

FDA response: Please submit the request for priority review with the full NDA package.

Additional FDA comment:

1. Please ensure your NDA submission includes a comprehensive summary of the clinical safety and pharmacokinetic data for subjects who received tecovirimat under expanded access and under other INDs (e.g. IND 116,039, IND (b) (4))

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our December 29, 2016 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on PDUFA V and the Program is available at
<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

In addition, we note that a chemistry pre-submission meeting is scheduled for February 28, 2017. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data*

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf>). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See <http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf>), as well as email access to the eData Team (cdeler-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review.

Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, [Study Data Standards Resources](#) and the CDER/CBER Position on Use of SI Units for Lab Tests website found at <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm>.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. Beginning **May 5, 2017**, the following submission types: **NDA, ANDA, BLA and Master Files** must be submitted in eCTD format. **Commercial IND** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: <http://www.fda.gov/ectd>.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

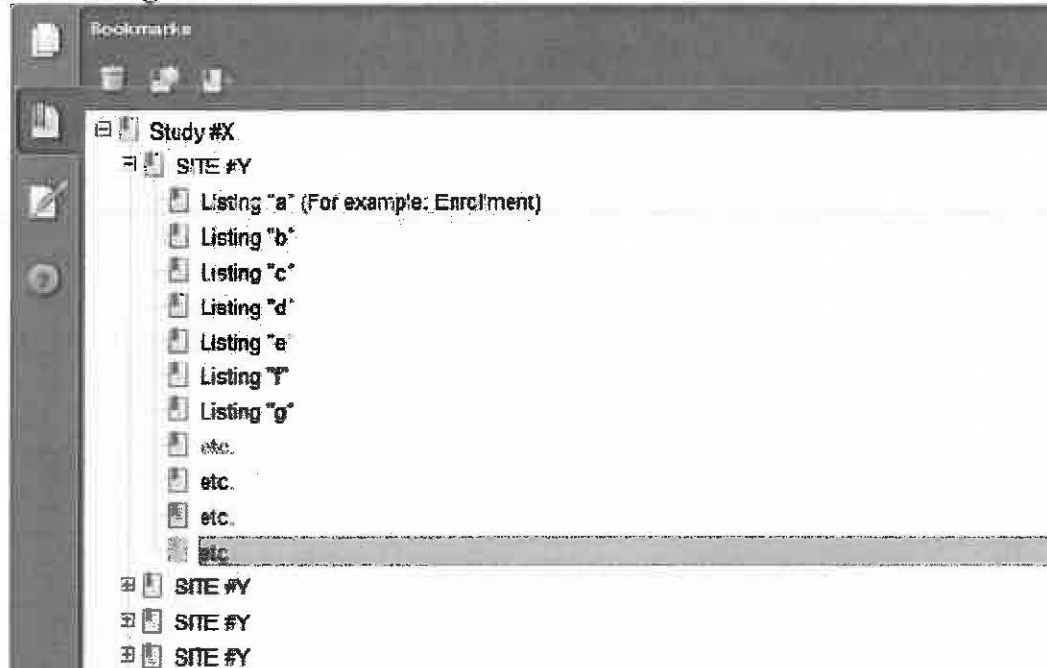
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation

- h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1

Technical Instructions:

Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

```

- [m5]
  - datasets
    - bimo
      - site-level
  
```

- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SOHAIL MOSADDEGH
01/11/2017