CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	(electronic stamp)
From	Edward Cox, MD MPH
Subject	Office Director Decisional Memo
NDA/BLA #	NDA 208627
Applicant Name	SIGA Technologies, Inc.
Date of Submission	December 8, 2017
PDUFA Goal Date	August 8, 2018
Proprietary Name / Established (USAN) Name	TPOXX tecovirimat
Dosage Forms / Strength	Capsule / 200 mg
Applicant Proposed Indication(s)/Populations	Treatment of adult and pediatric patients who have been infected with (b) (4)
Action:	Approval
Approved Indication(s)/Populations (if applicable)	TPOXX is indicated for the treatment of human smallpox disease caused by variola virus in adults and pediatric patients weighing at least 13 kg.

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer/Clinical Review	Kirk Chan-Tack
Statistical Review	Wen Zeng
Pharmacology Toxicology Review	L. Peyton Myers, David McMillan
OPQ Review	Ben Stevens, Balajee Shanmugam, Arwa El Hagrasy, Derek Smith, Elsbeth Chikhale, M. Scott Furness
Microbiology/Clinical Virology Review	Patrick Harrington
Clinical Pharmacology Review	Su-Young Choi, Ruojing Li, Qin Sun, Chao Liu. Shirley Seo
CDTL and Division Director Review	Adam Sherwat and Debbie Birnkrant

1. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

As a result of an intense global vaccination campaign and the specificity of smallpox for the human host, naturally occurring smallpox disease has not been detected since the late 1970s; the World Health Organization (WHO) declared smallpox eradicated from the world in 1980. Despite the eradication of naturally occurring smallpox, the virus that is the cause of smallpox is listed among the biological agents of concern regarding their potential biothreat uses. From our historical experience with smallpox, it is a serious and life-threatening disease caused by infection with variola virus, an orthopoxvirus. Historic mortality in variola major, the more common and serious form of smallpox, has been commonly cited at 30%. As routine smallpox vaccination in the U.S. ended in the 1970s, most of the U.S. population is susceptible to smallpox. Therefore, medical countermeasures, including antiviral therapies, are critically needed in the event of a smallpox outbreak. Tecovirimat, an orally bioavailable antiviral drug, was developed by the Applicant, SIGA Technologies, Inc., for the treatment of human smallpox.

The development of antiviral drugs for smallpox presents significant challenges. Because smallpox is a potentially serious and life-threatening disease but does not occur naturally, clinical efficacy trials in naturally occurring disease are not feasible, and human challenge studies in healthy subjects would be unethical to propose. Therefore, tecovirimat was developed under the Animal Rule (21 CFR part 314, subpart I), which supports a regulatory approval pathway in which studies using suitable animal models are the primary means for evaluating efficacy.

The Applicant conducted efficacy studies of tecovirimat in two well-studied, lethal animal models using non-variola, surrogate orthopoxviruses: non-human primates (NHPs) infected with monkeypox virus (MPXV), and rabbits infected with rabbitpox virus (RPXV). Treatment efficacy was clearly demonstrated in these animal models, which serve as disease models from which to extrapolate likely efficacy for the treatment of humans with smallpox, within the limitations of what is feasible given the marked species specificity of variola virus for the human host. Clinical pharmacokinetic (PK) and non-clinical PK/pharmacodynamic (PD) data were used to establish a human dosing regimen anticipated to be effective for the treatment of human smallpox in accordance with FDA's Guidance for Industry for Product Development Under the Animal Rule.

Based on the clinical data submitted in support of this New Drug Application (NDA), tecovirimat has an acceptable safety profile. In the pivotal safety trial (Study 246-008), most adverse events (AEs) were mild in severity, and AE rates were similar in the tecovirimat and placebo trial arms. There were no deaths or serious AEs (SAEs) judged to be related to tecovirimat. The safety database for tecovirimat is sufficient considering the seriousness of the indication and the limitations of feasible study.

The overall benefit-risk profile of tecovirimat is favorable for the treatment of smallpox disease even given the unavoidable residual uncertainty about its effects. In our decision to approve tecovirimat, we considered the available safety and efficacy data, the recommendation for approval by all review disciplines, and the unanimously favorable vote of the Antimicrobial Drugs Advisory Committee.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Smallpox is a disease caused by infection with variola virus. The historic mortality rate for variola major, the more common and serious form of smallpox, was variable but commonly cited at 30%.	Smallpox is a serious and life-threatening disease.
	Because of a successful intense global vaccination campaign, naturally occurring smallpox has been eradicated. The disease was declared eradicated from the world in 1980 by the WHO. Routine smallpox vaccination in the U.S. ended in the 1970s.	Most of the U.S. population is susceptible to smallpox if an exposure were to occur.
	Despite the eradication of naturally acquired smallpox, variola virus is categorized by the National Institute of Allergy and Infectious Diseases (NIAID) and Centers for Disease Control and Prevention (CDC) as a Category A priority pathogen.	Smallpox is categorized as a risk to national security and public health due to its bio-threat potential.
Current Treatment Options	There are no approved treatments for human smallpox.	An unmet medical need exists for treatment options for human smallpox disease in the event of accidental exposure to or intentional release of variola virus.
Benefit	Tecovirimat was developed under the Animal Rule which supports a regulatory approval pathway in which studies using suitable animal models are used to assess efficacy in animal models of infection to predict reasonable likelihood of efficacy in humans.	Because smallpox is a serious and life-threatening disease but does not occur naturally, clinical efficacy trials in naturally occurring disease are not feasible, and human challenge studies in healthy subjects would be unethical to propose.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	The Applicant conducted efficacy studies of tecovirimat in two well-studied, lethal animal models of infection using non-variola, surrogate orthopoxviruses: NHPs infected with MPXV and rabbits infected with RPXV. In the NHP/MPXV model, the appearance of skin lesions, which occurs by Day 4 post-viral challenge, was selected as a trigger for initiation of tecovirimat treatment. A statistically significant treatment benefit over placebo for the primary endpoint of mortality was demonstrated when tecovirimat was dosed at 3, 10, or 20 mg/kg/day for 14 days starting at Day 4 after virus inoculation. In the rabbit/RPXV model, fever, which consistently occurs by Day 4 post challenge, was selected as a trigger for initiation of tecovirimat treatment. A statistically significant treatment benefit over placebo for the primary endpoint of mortality was demonstrated when tecovirimat was dosed at 20, 40, 80, or 120 mg/kg/day for 14 days starting at day 4 after virus inoculation.	Treatment efficacy was clearly demonstrated in two lethal, well-studied animal models of non-variola orthopoxvirus infection with disease characteristics relevant to human smallpox.
	Treatment regimens of 10 mg/kg/day for 14 days in NHP/MPXV and 40 mg/kg/day for 14 days in rabbit/RPXV were selected as the fully effective dosing regimens for human dose selection. In determining the human dose, the PK of tecovirimat was compared between humans and animal models. The exposures in healthy humans using 600 mg BID x 14 days were higher than those associated with the fully effective doses in either NHP/MPXV or rabbit/RPXV.	Clinical PK and non-clinical PK/PD data were used to establish a human dosing regimen anticipated to be effective for the treatment of human smallpox.
	Studies in immunocompromised animal models have demonstrated reduced efficacy of tecovirimat.	Efficacy may be reduced in immunocompromised patients.
	Consistent with the animal rule, and considering the degree of uncertainty from the animal models of infection, if there is a smallpox event in the future a	A Postmarketing Requirement (PMR) will be

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	clinical trial of appropriate design could provide information to further inform on the effectiveness and safety of tecovirimat in humans with smallpox.	issued for the applicant to conduct a clinical trial of appropriate design to verify and describe the drug's clinical benefit and to assess its safety when used as indicated should there ever be a time when such a study is feasible and ethical
Risk	Nonclinical toxicology studies demonstrated a neurologic safety signal (e.g., convulsions, tremors, ataxia) which led to the adoption of a maximum allowable exposure level in clinical trials. Based on the clinical data submitted in support of this NDA, tecovirimat has an acceptable safety profile. In the pivotal safety trial, 359 healthy subjects received tecovirimat and 90 subjects received placebo. Most AEs were mild in severity, and AE rates were similar in the tecovirimat and placebo trial arms. There were no deaths or SAEs judged to be related to tecovirimat. No seizures or other significant neurological events were reported. The healthy population which composes the safety database may differ considerably from the person who would receive tecovirimat in the setting of a smallpox emergency.	A neurologic safety signal was demonstrated in nonclinical toxicology studies. Tecovirimat demonstrated an acceptable safety profile in clinical trials. A database of at least 300 individuals allows for reasonably reliable detection of adverse reactions occurring at a rate of 1% or greater. The safety database is sufficient for the proposed indication under the circumstances of development. As noted above, should there ever be a smallpox event in the future, an appropriately designed clinical trial will further inform on the safety of the product. Consistent with the Animal Rule, a PMR for such a study will accompany the approval action.
Risk Management	Tecovirimat has an acceptable safety profile.	Safety risks have not been identified that require risk management beyond standard pharmacovigilance in the event of drug use.

2. Further discussion to support regulatory action

Background

Tecovirimat is an antiviral drug that inhibits an orthopoxvirus VP37 envelope wrapping protein. It has been developed as an antiviral against variola virus, the etiologic agent of smallpox. Smallpox was declared eradicated by the World Health Organization (WHO) in 1980. Despite eradication of naturally occurring smallpox, variola virus is listed among the threat agents of concern regarding potential use as an agent of bioterrorism.

Tecovirimat was developed using the Animal Rule as the means to evaluate its efficacy. The animal rule was utilized because studies in humans naturally infected with variola virus are not feasible (as noted above, naturally occurring smallpox disease has been eradicated) and it would clearly not be ethical or feasible to study an antiviral drug in human challenge studies with such a dangerous pathogen. The efficacy evaluation of tecovirimat for the treatment of variola virus infection was based on studies in animal models of infection using surrogate orthopoxviruses. In addition to the unique constraints on use of live variola virus in animal models, the marked species specificity of variola virus for humans severely limits the utility of variola virus animal models of infection for evaluating tecovirimat's potential relevance as a treatment if human smallpox cases were to occur. However, the VP37 protein is highly conserved across orthopoxviruses. Hence, animal models of infection using other types of orthopoxviruses should be able to provide relevant information to assess the efficacy of tecovirimat against disease caused in those models by surrogate orthopoxviruses, as a means to predict a reasonable likelihood of clinical benefit if cases of human smallpox were ever to occur. The types of animal studies that could be used to demonstrate efficacy were discussed at an FDA public workshop (2009) and an FDA Antiviral Drugs Advisory Committee meeting (2011) and the tecovirimat animal studies are consistent with the discussions at the workshop and the advice from the FDA Advisory Committee. The assessment of efficacy using surrogate viruses in animal models of infection represents an exceptional approach necessitated by the unique circumstances inherent in studying a therapeutic for the treatment of variola virus, and leads to a residual degree of uncertainty regarding the compound's true effect if it had to be used for the intended purpose in humans. Nevertheless, after extensive discussion, the animal models were considered to provide the best feasible means to assess efficacy. These limitations underscore the importance of conducting an appropriately designed clinical trial should there ever be a smallpox event.

The review team has reviewed the issues in detail in their respective disciplines with regard to the safety and efficacy of tecovirimat. For a detailed discussion of NDA 208627, the reader is referred to the individual discipline specific reviews. In addition, the Cross-Discipline Team Leader's and Division Director's review summarize key issues in the NDA submission. This memorandum will focus on select issues from the review.

Product Quality

The TPOXX (tecovirimat) 200mg (b) (4) is recommended for approval from a product quality standpoint. Based on review of relevant information and from inspections, the manufacturing sites for the product are considered acceptable. The application is also acceptable from the standpoint of biopharmaceutics for this solid oral dosage form. The approval will include a post marketing commitment under which the applicant will conduct a risk assessment for elemental impurities when new batches of the product are manufactured.

Nonclinical Pharmacology/Toxicology

The recommendation from the pharmacology/toxicology reviewers is for approval. Repeat-dose general toxicology studies were conducted in mice, rats, dogs, and monkeys. No adverse drug-related findings were noted in the 3-month studies in mice and monkeys at the highest exposure doses (exposures were 24 and 2.7-fold the human exposure, respectively). In the 12-day rat study, findings were limited to the decreased body weight, food consumption, and mild liver toxicity consisting of increased liver weights in all treated animals, elevated bilirubin in the two highest dose groups and liver discoloration in the highest dose group. In two non-GLP 7-day toxicology studies in beagle dogs, neurotoxicity consisting of convulsions (tonic and clonic), tremors, ataxia, stereotypic walk, excessive blinking, face-twitching and jerky head movements were observed at an exposure multiple of 2.6 times that human dose. The exposure in dogs that led to neurotoxicity was considered in selecting the human dose in order to avoid human exposures at levels that were associated with neurotoxicity in dogs.

Clinical Virology

The Clinical Virology Reviewer recommends that the data in NDA 208627 support approval. Tecovirimat is an orthopoxvirus VP37 envelope wrapping protein inhibitor. The VP37 protein is highly conserved across orthopoxviruses. Tecovirimat resistance could be selected in multiple different orthopoxviruses in cell culture and was associated with VP37 amino acid substitutions. As noted in the product labeling, in cell culture assays the effective concentrations of tecovirimat resulting in a 50% reduction in virus induced cytopathic effect (EC50), were 0.016-0.067 µM, 0.014-0.039 µM, 0.015 µM, and 0.009 µM, for variola, monkeypox, rabbitpox, and vaccinia viruses, respectively. Ranges given for variola and monkeypox viruses are reflective of results from multiple strains assayed. The approval includes a postmarketing commitment to characterize tecovirimat antiviral activity against an expanded panel of variola virus isolates and recombinant vaccinia virus. Studies were also conducted to evaluate whether co-administration of tecovirimat with vaccinia virus (VACV) would affect vaccine immunogenicity or efficacy. From several studies conducted there was at least one NHP study where modestly reduced immunogenicity was observed; animals challenged with MPXV that had received tecovirimat along with VACV showed higher blood MPXV DNA levels.

Clinical Pharmacology

The Clinical Pharmacology reviewers recommend approval for NDA 208627. The human dose of tecovirimat 600 mg po BID is based upon the development of a dose/exposure-survival analysis relationship from the animal models of infection and translating the exposures to a human dose. Tecovirimat is recommended to be taken under fed conditions as the Cmax and AUC24 values were 31% and 41% higher, respectively under fed conditions. The dose that was selected for the human dose is approximately 2-fold, 2-fold, and 4-fold higher for Cmax, AUC 24hr, and Cmin as compared to the fully effective dose in NHPs. The human dose was also selected to avoid achieving human exposures at levels associated with neurotoxicity in the beagle dog studies. This process for selection of a human dose is consistent with the approach recommended in the Agency's Animal Rule guidance. It is also important that the data on dose and the labeled duration for tecovirimat dosing for humans based on extrapolation from animal models of infection using surrogate orthopoxviruses not be over interpreted because of a number of factors including:

- The target exposures are based on animal models of infection using surrogate orthopoxviruses. The exposures and durations of treatment needed to demonstrate efficacy in these animal models of infection may vary from a human with smallpox because of differences in the animals' immune defenses / intrinsic degree of susceptibility to the surrogate orthopoxviruses, and/or differences in exposures required to inhibit the surrogate orthopoxviruses compared to variola virus.
- The EC50 values vary for different orthopoxviruses and also vary for different variola virus isolates making it difficult to predict how the exposure will relate to any future smallpox infection in a human.
- The exposures attained are higher under fed conditions and it may be difficult for patients ill with smallpox to consume a meal sufficient to achieve the absorption of a person who is able to take tecovirimat under fed conditions. Very limited experience with a few patients who received tecovirimat for disseminated vaccinia infections found that the exposures attained were less than predicted.
- Development of resistance to various orthopoxviruses has been observed raising the possibility that lower exposures may increase the likelihood of developing resistance.

Hence, the recommended human dose and duration of treatment represents a reasonable approach, but the inherent uncertainty in this best feasible approach should be recognized and one should avoid over interpreting the data from animal models of infection.

The product labeling includes dosing for pediatric patients weighing at least 13 kg. The labeling also includes instructions for mixing the contents of an entire capsule or capsules in soft or liquid food for patients who cannot swallow capsules. In addition, there is also a Warning and Precautions statement regarding the potential for hypoglycemia with co-administration of repaglinide and tecovirimat.

Clinical/Statistical

The Clinical and Statistical reviewers recommend approval for NDA 208627.

Efficacy

Tecovirimat's efficacy was evaluated in animal models of lethal orthopoxvirus infections. These models included a non-human primate (cynomolgus macaques) monkeypox virus model and a rabbit (New Zealand White) rabbitpox virus infection model. Several different approaches were used to demonstrate the effects of tecovirimat against the surrogate orthopoxvirus infections including demonstration that there was a dose response, that earlier initiation of treatment achieved higher survival rates, and that increasing the duration of treatment generally leads to significantly higher survival rates than placebo treated controls. While there are inherent limitations when utilizing a surrogate orthopoxvirus in an animal model of infection, the fact that the VP37 target is highly conserved across orthopoxviruses helps support the decision to utilize surrogate orthopoxviruses to assess likelihood of treatment benefit for this Category A pathogen. In addition, given the characteristics of variola virus (including its marked species specificity for humans and the constraints on its use in experiments) the use of surrogate orthopoxviruses is a reasonable means to assess the likelihood of efficacy of tecovirimat as a therapeutic for human smallpox infection.

Safety

The safety database for tecovirimat contains data from 788 subjects who received tecovirimat, including 437 who received the dose of 600 mg po BID (78 subjects in phase 1 studies and 359 subjects in Study 246-008, a randomized, double-blind study to evaluate the safety of the 600 mg BID, 14-day regimen that enrolled 359 patients in the tecovirimat arm and 90 patients in the placebo arm). Most of the ADRs that were reported were mild in severity. Treatment-emergent ADRs reported in ≥ 2% of subjects are summarized in the table below.

Adverse Reaction	**Tecovirimat N=359**	**Placebo N=90**
Headache	44 (12%)	7 (8%)
Nausea	16 (5%)	4 (4%)
Abdominal Pain	7 (2%)	1 (1%)
Vomiting	7 (2%)	0 (0%)
Diarrhea	7 (2%)	2 (2%)

There was one death in Study 246-008 (the only SAE in the trial). The death was due to a pulmonary embolism in a 46-year old woman with a history of lower extremity deep venous thrombosis and concomitant use of Depo-Provera, and occurred 7 days after completing her 14-day course of tecovirimat. The safety information on tecovirimat is described in the product labeling.

Advisory Committee Meeting

NDA 208617 was presented to the FDA's Antimicrobial Drugs Advisory Committee on May 1, 2018. The committee voted 17 Yes; 0 No that based on the available data, the risk-benefit profile of tecovirimat supports its use for the treatment of human smallpox.

Pediatrics

Pediatric studies have not been performed because of ethical considerations. Dosing for pediatric patients is included in the product labeling based on modeling and simulation. Given the nature of smallpox disease and the inability to obtain pediatric data, developing dosing recommendations for pediatric patients based on modeling and simulation is a reasonable approach.

Postmarketing Requirements and Commitments

The following postmarketing requirement and commitments are included in the approval letter for this Subpart I approval (excerpted from the approval letter).

SUBPART I APPROVAL REQUIREMENTS

Approvals under 21 CFR Part 314, Subpart I (Approval of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible) are subject to three requirements:

1. *Approval with restrictions to ensure safe use.* This subsection permits the Agency to require postmarketing restrictions as are needed to ensure safe use of the drug product, commensurate with the specific safety concerns presented by the drug product. We have concluded that TPOXX® (tecovirimat) can be safely used without restrictions on distribution or use.

2. *Information to be provided to patient recipients.* This subsection requires applicants to prepare labeling to be provided to patient recipients for drug products approved under this subpart. We conclude that the FDA-Approved Patient Labeling and Instructions For Use for TPOXX (tecovirimat) meets the requirements of this subsection. We remind you that the patient labeling and instructions for use must be available with the product to be provided, when possible, prior to administration or dispensing of the drug product for the use approved under this subpart.

3. *Postmarketing Studies.* This subsection requires you to conduct postmarketing studies, such as field studies, to verify and describe the drug's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical.

Therefore, you are required to conduct the following postmarketing study, when feasible and ethical, to meet the Subpart I approval requirements:

3417-1 Conduct a Field Study to evaluate the clinical response, drug concentrations, and safety profile of tecovirimat when used in the treatment of subjects with variola virus infection.

We refer to your submission dated April 25, 2018, outlining your plan to conduct this field study to meet the postmarketing requirement and your submission, dated June 8, 2018, stating that you will submit a protocol according to the following schedule:

Draft Protocol Submission:	02/2019
Final Protocol Submission:	06/2019

Submit final reports to this NDA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart I Postmarketing Requirements**."

REQUIRED PEDIATRIC ASSESSMENTS

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 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 this requirement.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

3417-2 Conduct a human factors validation study to demonstrate that representative users (e.g. healthcare providers and lay users) can safely and effectively prepare and administer tecovirimat to pediatric patients requiring less than a 200 mg dose (i.e. less than 1 full capsule) under simulated use conditions that are representative of realistic use conditions.

The timetable you submitted on June 18, 2018 states that you will conduct this study according to the following schedule:

Final Protocol Submission:	01/2020
Study/Trial Completion:	06/2020
Final Report Submission:	12/2020

3417-3 Conduct cell culture studies to characterize tecovirimat antiviral activity against an expanded panel of variola virus isolates and recombinant vaccinia viruses. These studies should capture the known VP37 amino acid heterogeneity in variola viruses, as well as a common orthopoxvirus VP37 polymorphism, and should also include multiple independent isolates with identical VP37 amino acid sequences, when feasible.

The timetable you submitted on May 23, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	01/2019
Final Protocol Submission:	05/2019
Study/Trial Completion:	09/2020
Final Report Submission:	12/2020

3417-4 Conduct a study to determine the pharmacokinetics of tecovirimat in subjects with body weight greater than 120 kilograms (>120 kg) and to further determine if a change in dosing regimen is needed in these subjects.

The timetable you submitted on June 1, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	04/2019
Final Protocol Submission:	07/2019
Study/Trial Completion:	08/2020
Final Report Submission:	02/2021

3417-5 Conduct an in vitro study to determine the potential for a drug interaction between tecovirimat and phosphate binders. If the results of the study are inconclusive or indicate binding of phosphate binders to tecovirimat is significant, conduct an in vivo study to determine the magnitude of interaction to inform the dosing regimen in patients who concomitantly take phosphate binders.

The timetable you submitted on June 1, 2018, states that you will conduct this study according to the following schedule:

Draft Protocol Submission:	04/2019
Final Protocol Submission:	07/2019
Study/Trial Completion:	08/2020
Final Report Submission:	02/2021

POSTMARKETING COMMITMENTS NOT SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitment:

3417-6 Conduct and submit a risk assessment for elemental impurities when new batches of the drug product are manufactured. This information should be submitted as a Changes Being Effected-30 Supplement.

The timetable you submitted on April 20 2018, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	NA
Study/Trial Completion:	To be determined when new drug product batches are to be manufactured.
Final Report Submission:	To be determined when new drug product batches are to be manufactured.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EDWARD M COX
07/13/2018