CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210864Orig1s000

PRODUCT QUALITY REVIEW(S)

QUALITY ASSESSMENT

Recommendation: Approve

NDA 210864

Review # 3

Drug Name/Dosage Form	Sesquient™ (fosphenytoin sodium) injection
Strength	50 mg PE/mL*
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Sedor Pharmaceuticals, LLC
US agent, if applicable	N/A

***** PE is fosphenytoin sodium equivalents.

Quality Review Team*

DISCIPLINE	REVIEWER	SECONDARY REVIEWER
Drug Product/Labeling	Andrei Ponta	Julia Pinto
Manufacturing	Peter Krommenhoek	Nallaperumal Chidambaram
Regulatory Business Process Manager	Kelly Ballard	--
Application Technical Lead	Martha Heimann	--

* Disciplines involved in current review cycle.

SUBMISSIONS REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD-029, Resubmission after complete response	5/8/2020	Drug product, Manufacturing

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II	(b) (4)	Fosphenytoin sodium	Adequate	10/12/2018	Reviewed by S. Chandramouli
	IV		(b) (4)	N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	

[1] Adequate information in application or no changes to information since previous reviews.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20450	Cerebyx (fosphenytoin sodium injection). Referenced under 505(b)(2) for safety and efficacy of fosphenytoin sodium.
IND	74871	Development of fosphenytoin sodium with Captisol.

2. CONSULTS: N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

The Office of Product Quality (OPQ) review team recommends that the Agency **APPROVE** NDA 210864 for Sesquient® (fosphenytoin sodium) injection. From a quality perspective, the Applicant has adequately addressed all quality deficiencies conveyed in the December 20, 2019 complete response letter (CRL).

II. Summary of Quality Assessments

A. Product Overview

Fosphenytoin sodium is a water-soluble prodrug for phenytoin that was developed as an alternative to Dilantin® (phenytoin sodium injection). It was first marketed in 1996 by Parke-Davis Pharmaceuticals (now Pfizer) as Cerebyx® injection (NDA 20450, approved 1996). The Applicant, Sedor Pharmaceuticals (Sedor), has submitted a 505(b)(2) application that references the Cerebyx NDA to support safety and efficacy of fosphenytoin. The primary differences between the proposed product, Sesquient, and Cerebyx are the addition of a cyclodextrin derivative, betadex sulfobutyl ether sodium (Captisol®) and a slight pH reduction (target pH 8.0). Unlike Cerebyx, which requires refrigeration, Sesquient is intended to be stored at room temperature.

Proposed Indication(s) including Intended Patient Population	Treatment of generalized tonic-clonic status epilepticus, prevention and treatment of seizures occurring during neurosurgery, and short-term use as a substitute for oral phenytoin when oral administration is not possible in adult and pediatric patients.
Duration of Treatment	Short-term
Maximum Daily Dose	Maximum loading dose: 20 mg PE/kg Maintenance: 6 mg/kg
Alternative Methods of Administration	Loading doses have been given by the IM route when IV access is not possible.

B. Quality Assessment Overview

NDA 210864 was originally submitted on May 22, 2018. On March 22, 2019, the Agency issued a CRL due to product quality and clinical deficiencies. The deficiencies conveyed in the March 22, 2019, CRL were related to the drug product and the manufacturing process. The Applicant addressed all but one of the quality deficiencies in the June 28, 2019, resubmission (SD-20). A second CRL was issued on December 20, 2019. Refer to the Integrated Quality Reviews dated February 26, 2019, and December 19, 2019, for further details.

Drug Substance: Adequate

There were no outstanding deficiencies related to the bulk drug substance, and no new information was submitted in the resubmission.

Drug Product: Adequate

During the review of the original NDA, the review team identified deficiencies related to and communicated deficiencies related to observation of visible foreign particles, including particles greater than (b) (4) during inspection of stability samples for evidence of (b) (4). The Applicant did not determine the root cause for the observed particles or propose an adequate risk mitigation strategy. In the June 28, 2019 resubmission, the Applicant initially characterized the particles as likely resulting from (b) (4) equipment, and thus intrinsic to the manufacturing process. This explanation was deemed not consistent with the types of particles (b) (4) identified by (b) (4). Subsequently, the Applicant submitted results of additional testing performed by a second laboratory, (b) (4), on aged samples. (b) (4) detected some (b) (4) particles, which would be consistent with the container closure system, but did not detect other foreign particles. Based on the (b) (4) report, the Applicant contended that the foreign particles observed by (b) (4) were most likely the result of contamination due to environmental conditions at the (b) (4) site. The Applicant did not provide any other information that would support this conclusion. The following Drug Product and Manufacturing deficiency was conveyed in the December 20, 2019 CRL.

> *It is crucial from a safety perspective that the drug product does not contain foreign particles. Information provided to date has not adequately addressed this drug product quality issue.*
>
> *In a quality information amendment submitted on December 6, 2019, you provided additional study results from (b) (4) regarding particles in the drug product. You concluded that the initial particulate information, obtained in association with the (b) (4), was erroneous and not representative of the drug product due to testing environment conditions. However, there is not sufficient information (e.g., documentation of environmental conditions at (b) (4) when the (b) (4) testing was performed) to confirm that the initial results from the (b) (4) study are erroneous. Thus, the (b) (4) study report does not conclusively support your contention that the root cause for the particulates observed and characterized by (b) (4) in your drug product is laboratory error, and we are unable to disregard the (b) (4) results.*
>
> *Characterize the particles observed in the drug product and identify the root cause of their presence (e.g., container closure system, testing method/conditions, manufacturing equipment), and provide a Risk Mitigation & Control Plan to mitigate the presence of particulates in your drug product. Provide data demonstrating that the actions taken will prevent reoccurrence of particles in the drug product.*

As part of the resubmission, the Applicant provided a root cause analysis investigating the particulate testing and results from (b) (4) and (b) (4). This investigation considered whether procedural differences between the two labs (e.g., environmental conditions, personnel, equipment, test samples, and methods) could have caused the differences in results. As a result of the investigation the Applicant noted several differences between the sites. The most significant differences relate to environmental conditions, types of testing performed, and sampling procedures.

(b) (4)

Based on the findings of the root cause investigation and the more rigorous testing procedures at (b) (4), it is reasonable to conclude that environmental cross-contamination may have occurred during testing at (b) (4). Thus, the data obtained from (b) (4), which indicate that the drug product does not contain any (b) (4) particles, are considered valid.

Manufacturing: Adequate

(b) (4)

Microbiology: Adequate

There were no outstanding microbiology deficiencies, and no new information was submitted in the resubmission.

Environmental: Adequate

The Applicant submitted an acceptable claim for categorical exclusion under 21 CFR § 25.31(a)

Labeling: Adequate

As noted in previous reviews, product labeling for Sesquient should identify product characteristics that differ from the current USP monograph requirements for Fosphenytoin Sodium Injection. Recommended labeling revisions have been communicated to the clinical division and incorporated into draft labeling.

C. Final Risk Assessment for Sesquient (fosphenytoin sodium) Injection

From Initial Risk Identification			Review Assessment	
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**
Appearance	Formulation Container closure Raw materials Process parameters Scale Equipment Site	**L**	(b) (4)	Adequate
Assay, stability		**L**		Adequate
Sterility		**H**		Adequate
Endotoxin, pyrogen		**M**		
Fill volume		**L**		Adequate
Osmolality		**L**		Adequate
pH		**L**		Adequate
Particulate matter		**M**		Adequate
Leachable/Extractables		**L**		Adequate

D. List of Deficiencies to be Communicated

Not applicable.

Application Technical Lead Name and Date:

Martha R. Heimann, Ph.D.

CMC Lead
Office of New Drug Products
Division of New Drug Products II

10/15/2020

Martha Heimann

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LABELING

I. Package Insert

(b) (4)

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	SESQUIENT, Fosphenytoin Injection *Reviewer's Note:* (b) (4)
Dosage form, route of administration	Injection, IV

Controlled drug substance symbol	NA
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	10 mL single-dose injection, containing 500 mg PE 2 mL single-dose injection, containing 100 mg PE *Reviewer's Note: Applicant will be asked to update PI to indicate that the (b) (4) strength contains 2 mL*

2. *Section 2 Dosage and Administration*

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions to Avoid Dosing Errors

Use caution when administering TRADE NAME because of the risk of dosing errors *[see Warnings and Precautions (5.1)]*.

Phenytoin Sodium Equivalents (PE)
The dose, concentration, and infusion rate of TRADE NAME should always be expressed as phenytoin sodium equivalents (PE). There is no need to perform molecular weight-based adjustments when converting between fosphenytoin and phenytoin sodium doses. TRADE NAME should always be prescribed and dispensed in phenytoin sodium equivalent units (PE). The amount and concentration of fosphenytoin is always expressed in terms of mg of phenytoin sodium equivalents (mg PE).

Concentration of 50 mg PE/mL
Do not confuse the concentration of TRADE NAME with the total amount of drug in the vial.

Errors, including fatal overdoses, have occurred when the concentration of the vial (50 mg PE/mL) was misinterpreted to mean that the total content of the vial was 50 mg PE. These errors have resulted in two- or tenfold overdoses of TRADE NAME since each of the vials actually contains a total of 100 mg PE ((b) (4)) or 500 mg PE (10 mL (b) (4)). Ensure the appropriate volume of TRADE NAME is withdrawn from the vial when preparing the dose for administration. Attention to these details may prevent some TRADE NAME medication errors from occurring.

2.2 Preparation

Prior to intravenous (b) (4) infusion, dilute TRADE NAME in 5% dextrose or 0.9% saline solution for injection to a concentration ranging from 1.5 to 25 mg PE/mL. The maximum concentration of TRADE NAME in any solution should be 25 mg PE/mL. When TRADE NAME is given as an intravenous infusion, TRADE NAME needs to be diluted and should only be administered at a rate not exceeding 150 mg PE/min.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

(b) (4)

For single-dose only. After opening, any unused product should be discarded.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	The drug product can be administered via intravenous (IV) infusion at concentrations ranging from 1.5 to 25 mg PE/mL. The drug product is to be diluted in 5% dextrose or 0.9% saline. In-use stability studies demonstrated that the drug product is compatible with IV bags and infusion lines (tubing) for up to 4 hours, the longest possible exposure time. After opening, any unused product should be discarded.

3. *Section 3 Dosage Forms and Strengths*

3 DOSAGE FORMS AND STRENGTHS

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Injection
Strengths: in metric system	10 mL single-dose injection, containing 500 mg PE 2 mL single-dose injection, containing 100 mg PE *Reviewer's Note: Applicant will be asked to update PI to indicate that the* (b) (4) *strength contains 2 mL*
Active moiety expression of strength with equivalence statement (if applicable)	NA
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Clear, colorless solution (b) (4) *Reviewer's Note:* (b) (4)

4. *Section 11 Description*

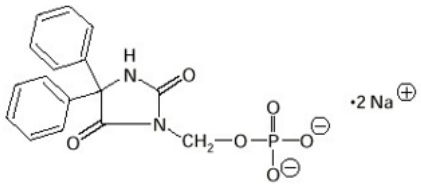
11 DESCRIPTION

(b) (4) Fosphenytoin Sodium Injection (TRADE NAME) is a prodrug intended for parenteral administration; its active metabolite is phenytoin. 1.5 mg of fosphenytoin sodium is equivalent to 1 mg phenytoin sodium, and is referred to as 1 mg phenytoin sodium equivalents (PE). The amount and concentration of fosphenytoin is always expressed in terms of mg PE.

The pharmacological class of the fosphenytoin sodium is hydantoin derivative, and the therapeutic class is anticonvulsant.

(b) (4)

The chemical name of fosphenytoin is 5,5-diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt. The molecular structure of fosphenytoin is:



The molecular weight of fosphenytoin is 406.24.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	SESQUIENT, Fosphenytoin Injection
Dosage form and route of administration	Injection, IV
Active moiety expression of strength with equivalence statement (if applicable)	NA
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Sulfobutyl ether beta-cyclodextrin (100 mg/mL), tromethamine (2.42 mg/mL), hydrochloric acid, and sodium hydroxide *Reviewer's Note: Applicant will be asked to include the quantity of each inactive ingredient and list the inactive ingredients in alphabetical order and to refer to excipients by nonproprietary name only*
Statement of being sterile (if applicable)	Sterile
Pharmacological/ therapeutic class	Anticonvulsant
Chemical name, structural formula, molecular weight	$C_{16}H_{13}N_2Na_2O_6P$, 406.24 Da *Reviewer's Note: Applicant will be asked to include sodium after fosphenytoin as the structure and molecular weight correspond*

	to the sodium salt.
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	*Reviewer's Note: Applicant will be asked to include the following statements as the drug product does not comply with the current USP monograph for fosphenytoin sodium injection label: FDA approved impurity specification for phenytoin differs from USP. FDA approved pH specification differs from USP.*

5. *Section 16 How Supplied/Storage and Handling*

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

TRADE NAME is a clear, colorless, sterile solution supplied as follows:

(b) (4)

[redacted]

TRADE NAME should always be prescribed in phenytoin sodium equivalents (PE) *[see Dosage and Administration (2.1) and Warnings and Precautions (5.1)]*.

1.5 mg of fosphenytoin sodium is equivalent to 1 mg phenytoin sodium, and is referred to as 1 mg PE. The amount and concentration of fosphenytoin is always expressed in terms of mg of phenytoin sodium equivalents (PE). Fosphenytoin's weight is expressed as phenytoin sodium equivalents to avoid the need to perform molecular weight-based adjustments when substituting fosphenytoin for phenytoin or vice versa.

16.2 Storage and Handling

Store TRADE NAME at room temperature. Temperature excursions are permitted between 15-30°C (59-86°F). [see USP Controlled Room Temperature]. Vials that develop particulate matter should not be used.

Injection vials are single-dose only. After opening, any unused product should be discarded.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	

Strength of dosage form	10 mL single-dose injection, containing 500 mg PE 2 mL single-dose injection, containing 100 mg PE
Available units (e.g., bottles of 100 tablets)	10 mL and (b) (4) vial
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC number not included
Special handling (e.g., protect from light)	After opening, any unused product should be discarded.
Storage conditions	CRT
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Emergent BioSolutions Inc

Reviewer's Assessment of Package Insert: ***Inadequate***

- Revisions identified and will be communicated to the Applicant.

II. Labels:

1. ***Container and Carton Labels***

(b) (4)

[redacted]

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Andrei Ponta

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Julia Pinto

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/s/

MARTHA R HEIMANN
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QUALITY ASSESSMENT

Recommendation: Complete Response

NDA 210864
Review # 2

Drug Name/Dosage Form	Sesquient™ (fosphenytoin sodium) injection
Strength	50 mg PE/mL*
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Sedor Pharmaceuticals, LLC
US agent, if applicable	N/A

* PE is fosphenytoin sodium equivalents.

Quality Review Team*

DISCIPLINE	REVIEWER	SECONDARY REVIEWER
Drug Product/Labeling	Andrei Ponta	Julia Pinto
Manufacturing	Peter Krommenhoek	Nallaperumal Chidambaram
Regulatory Business Process Manager	Dahlia A. Woody	--
Application Technical Lead	Martha Heimann	--

* Disciplines involved in current review cycle.

SUBMISSIONS REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD-017, Response to IR [1]	3/14/2019	Drug product, Manufacturing
SD-018, Response to IR [2]	3/22/2019	
SD-020, Resubmission	6/28/2019	
SD-022, Response to IR	9/12/2019	
SD-024, Response to IR	10/23/2019	
SD-025, Response to IR	10/28/2019	
SD-026, Response to IR	11/27/2019	
SD-027, Quality amendment	12/6/2019	

[1] Review was deferred during first cycle,
[2] Amendment was received after action letter issued.

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II	(b) (4)	Fosphenytoin sodium	Adequate	10/12/2018	Reviewed by S. Chandramouli
	IV		(b) (4)	N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	

[1] Adequate information in application or no changes to information since previous reviews.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20450	Cerebyx (fosphenytoin sodium injection). Referenced under 505(b)(2) for safety and efficacy of fosphenytoin sodium.
IND	74871	Development of fosphenytoin sodium with Captisol.

2. CONSULTS: N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

The Office of Product Quality (OPQ) review team recommends that the Agency issue a second **Complete Response Letter** (CRL) for NDA 210864 for Sesquient® (fosphenytoin sodium) injection. From a quality perspective, the Applicant has not adequately addressed all quality deficiencies conveyed in the March 22, 2019 CRL.

II. Summary of Quality Assessments

A. Product Overview

Fosphenytoin sodium is a water-soluble prodrug for phenytoin that was developed as an alternative to Dilantin® (phenytoin sodium injection). It was first marketed in 1996 by Parke-Davis Pharmaceuticals (now Pfizer) as Cerebyx® injection (NDA 20450, approved 1996). Note that labeling for Cerebyx, and its generic equivalents, is expressed as the equivalent amount of phenytoin sodium equivalents (PE)/mL. Fosphenytoin Sodium Injection offers an advantage of fewer injection site reactions versus Phenytoin Sodium Injection. Solubilizing phenytoin requires use of alcohol and propylene glycol) as co-solvents and strongly alkaline conditions (solution pH 10 – 12). However, while fosphenytoin sodium is highly water soluble and can be formulated under less alkaline conditions (pH 8.6 – 9.0), Fosphenytoin Sodium Injection requires refrigeration to minimize degradation.

The Applicant, Sedor Pharmaceuticals (Sedor), has submitted a 505(b)(2) application that references the Cerebyx NDA to support safety and efficacy of fosphenytoin. The primary differences between the proposed product, Sesquient, and Cerebyx are the addition of a cyclodextrin derivative, betadex sulfobutyl ether sodium (Captisol®) and a slight pH reduction (target pH 8.0). The resulting formulation is intended to be stored at room temperature, rather than refrigerated.

Proposed Indication(s) including Intended Patient Population	Treatment of generalized tonic-clonic status epilepticus, prevention and treatment of seizures occurring during neurosurgery, and short-term use as a substitute for oral phenytoin when oral administration is not possible in adult and pediatric patients.
Duration of Treatment	Short-term
Maximum Daily Dose	Maximum loading dose: 20 mg PE/kg Maintenance: 6 mg/kg
Alternative Methods of Administration	Loading doses have been given by the IM route when IV access is not possible.

B. Quality Assessment Overview

Drug Substance

There were no outstanding deficiencies related to the bulk drug substance, and no new information was submitted in the resubmission.

Drug Product

During the review of the original NDA, the review team identified and communicated deficiencies related to:

1. Inadequate validation of the HPLC method used to monitor degradation products at release and on stability. This deficiency precluded review of the primary stability data or establishment of a shelf life for the product.
2. Inadequate "in-use" studies to support compatibility of the product with labeled IV diluents
3. Observation of visible foreign particles, including particles greater than (b) (4) during inspection of stability samples for evidence of (b) (4) The Applicant did not determine the root cause for the observed particles or propose an adequate risk mitigation strategy.

The Applicant has addressed the first deficiency by revalidating the HPLC method and agrees to accept a shorter shelf life, i.e., 12 months for product stored at controlled room temperature. The Applicant has also provided results from additional in-use dilution studies to demonstrate compatibility with all IV diluents identified in the product labeling. However, the Applicant has not adequately addressed the issue of foreign particles. The firm initially characterized the particles as likely resulting from (b) (4) (b) (4) equipment, and thus intrinsic to the manufacturing process. This explanation was deemed not consistent with the types of particles (b) (4) . It is also not consistent with the manufacturing process, (b) (4) Subsequently, the Applicant submitted results from additional testing performed by (b) (4) . In the second study, (b) (4) identified (b) (4) particles (up to (b) (4)) but did not find (b) (4) particles. Based on the (b) (4) report, the Applicant now attributes the initial observation of foreign particles to environmental conditions at the (b) (4) testing but has not provided any other information that would support this conclusion. In the absence of such information, it is not possible to disregard the original (b) (4) test results. As the presence of foreign particles is considered a potential safety concern for a product administered by the IV route, the review team recommends that the application not be approved until the identifies the root cause and establishes procedures to prevent contamination of future product batches.

C. Special Product Quality Labeling Recommendations

As noted in the previous review, due to differences between the proposed specification and storage condition for Sesquient and the current USP monograph for Fosphenytoin Sodium Injection, labeling would need to state the differences between Sesquient and the USP monograph until the monograph is revised. This was not an approvability issue.

D. Final Risk Assessment for Sesquient (fosphenytoin sodium) Injection

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**First Cycle Risk Evaluation**	**Second Cycle Risk Evaluation**
Appearance	• Formulation • Container closure • Raw materials • Process parameters • Scale • Equipment • Site	**L**	(b) (4)	Adequate	No change
Assay, stability		**L**		**Inadequate**	Adequate
Sterility		**H**		Adequate	No change
Endotoxin, pyrogen		**M**			
Fill volume		**L**		Adequate	No change
Osmolality		**L**		Adequate	No change
pH		**L**		Adequate	No change
Particulate matter		**M**		**Inadequate**	**Inadequate**
Leachable/Extractables		**L**		Adequate	No change

E. List of Deficiencies to be Communicated

It is crucial from a safety perspective that the drug product does not contain foreign particles. Information provided to date has not adequately addressed this drug product quality issue.

In a quality information amendment submitted on December 6, 2019, you provided additional study results from (b) (4) *regarding particles in the drug product. You concluded that the initial particulate information, obtained in association with the* (b) (4) *testing at* (b) (4)*, was erroneous and not representative of the drug product due to testing environment conditions. However, there is not sufficient information (e.g., documentation of environmental conditions at* (b) (4) *when the* (b) (4) *testing was performed) to confirm that the initial results from the* (b) (4) *study are erroneous. Thus, the* (b) (4) *study report does not conclusively support your contention that the root cause for the particulates observed and characterized by* (b) (4) *in your drug product is laboratory error and we are unable to disregard the* (b) (4) *results.*

Characterize the particles observed in the drug product and identify the root cause of their presence (e.g. container closure system, testing method/conditions, manufacturing equipment), and provide a Risk Mitigation & Control Plan to mitigate the presence of particulates in your drug product. Provide data demonstrating that the actions taken prevent reoccurrence of particles in the drug product.

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/s/

MARTHA R HEIMANN
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Recommendation: Complete Response

NDA 210864

Review # 1

Drug Name/Dosage Form	Sesquient™ (fosphenytoin sodium) injection
Strength	50 mg PE/mL*
Route of Administration	Intravenous
Rx/OTC Dispensed	Rx
Applicant	Sedor Pharmaceuticals, LLC
US agent, if applicable	N/A

***** PE is fosphenytoin sodium equivalents.

Quality Review Team

DISCIPLINE	REVIEWER	SECONDARY REVIEWER
Drug Substance	Sithamalli Chandramouli	Su Tran
Drug Product/Labeling	Andrei Ponta	Wendy Wilson-Lee
Process	Peter Krommenhoek	Nallaperumal Chidambaram
Microbiology	Avital Shimanovich	Marla Stevens-Riley
Facility	Peter Krommenhoek	Vidya Pai
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Dahlia A. Woody	--
Application Technical Lead	Martha Heimann	--
Laboratory (OTR)	N/A	
ORA Lead	N/A	
Environmental Analysis (EA)	N/A	

SUBMISSIONS REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
SD-001, Original NDA	5/22/2018	All
SD-004, Response to IR	6/29/2018	Drug Substance, Product, Process, Facility
SD-006, Response to IR	7/13/2018	Process
SD-009, Response to IR	10/29/2018	Microbiology
SD-010, Response to IR	11/16/2018	Product
SD-011, Response to IR	12/7/2018	Product, Microbiology
SD-014, Response to IR	1/15/2019	Product, Microbiology

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II	(b) (4)	Fosphenytoin sodium	Adequate	10/12/2018	Reviewed by S. Chandramouli
	IV		(b) (4)	N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	
	III			N/A [1]	N/A [1]	

[1] Adequate information in application or no changes to information since previous reviews.

B. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20450	Cerebyx (fosphenytoin sodium injection). Referenced under 505(b)(2) for safety and efficacy of fosphenytoin sodium.
IND	74871	Development of fosphenytoin sodium with Captisol.

2. CONSULTS: N/A

Executive Summary

I. Recommendations and Conclusion on Approvability

The Office of Product Quality (OPQ) review team recommends that the Agency issue a **Complete Response Letter** for NDA 210864 for Sesquient® (fosphenytoin sodium) injection. From a quality perspective, the application does not include adequate information to ensure that the applicant can consistently manufacture a product that is suitable for use to treat the intended patients.

II. Summary of Quality Assessments

A. Product Overview

Fosphenytoin sodium is a water-soluble prodrug for phenytoin that was developed as an alternative to Dilantin® (phenytoin sodium injection). It was first marketed in 1996 by Parke-Davis Pharmaceuticals (now Pfizer) as Cerebyx® injection (NDA 20450, approved 1996). Note that labeling for Cerebyx, and its generic equivalents, is expressed as the equivalent amount of phenytoin sodium equivalents (PE)/mL. Fosphenytoin Sodium Injection offers an advantage of fewer injection site reactions versus Phenytoin Sodium Injection. Solubilizing phenytoin requires use of alcohol and propylene glycol) as co-solvents and strongly alkaline conditions (solution pH 10 – 12). However, while fosphenytoin sodium is highly water soluble and can be formulated under less alkaline conditions (pH 8.6 – 9.0), Fosphenytoin Sodium Injection requires refrigeration to minimize degradation.

The applicant, Sedor Pharmaceuticals (Sedor), has submitted a 505(b)(2) application that references the Cerebyx NDA to support safety and efficacy of fosphenytoin. The primary differences between the proposed product, Sesquient, and Cerebyx are the addition of a cyclodextrin derivative, betadex sulfobutyl ether sodium (Captisol®) and a slight pH reduction (target pH 8.0). The resulting formulation is intended to be stored at room temperature, rather than refrigerated.

Proposed Indication(s) including Intended Patient Population	Treatment of generalized tonic-clonic status epilepticus, prevention and treatment of seizures occurring during neurosurgery, and short-term use as a substitute for oral phenytoin when oral administration is not possible in adult and pediatric patients.
Duration of Treatment	Short-term
Maximum Daily Dose	Maximum loading dose: 20 mg PE/kg Maintenance: 6 mg/kg
Alternative Methods of Administration	Loading doses have been given by the IM route when IV access is not possible.

B. Quality Assessment Overview

Drug Substance

The bulk active pharmaceutical ingredient (API), Fosphenytoin Sodium USP, is a well characterized, small molecule that is very soluble in water. The bulk drug substance is manufactured by (b) (4). Information regarding the characterization, manufacture, and control of the API is incorporated by cross-reference to drug master file (DMF) (b) (4). The DMF was reviewed to support this NDA and is deemed adequate. Information submitted by the applicant directly to the NDA includes a summary of general properties, (b) (4) potential impurities, and the applicant's acceptance specification, which meets, or exceeds, USP monograph requirements. Where applicable, analytical procedures are based on the USP monograph and general USP compendial methods. Noncompendial methods are adequately described and validated.

Drug Product

Sesquient injection is a sterile, preservative-free, aqueous solution that contains fosphenytoin sodium 75 mg/mL (equivalent to phenytoin sodium 50 mg/mL). In addition to Captisol, the solution contains tromethamine (b) (4), and may contain hydrochloric acid or sodium hydroxide (as needed to adjust pH). The product will be packaged in (b) (4) glass vials with (b) (4) rubber seals and flip-off over-seals containing 2 mL (100 mg PE) or 10 mL (500 mg PE).

The manufacturing process for Sesquient injection consists of: (b) (4) However, particulate matter, which included some particles larger than (b) (4) was observed in stability samples. The presence of such particles is considered a potential safety concern for a product administered by the IV route. The manufacturer's root-cause investigation concludes that the observed particles result from (b) (4) manufacturing equipment and container components (b) (4) The presence of (b) (4) particles in the final drug product is concerning. Additional information regarding the applicant's proposed mitigation strategy for (b) (4) particles is needed.

There are several differences between the proposed product specification and the current USP monograph for Fosphenytoin Sodium Injection. The applicant proposes use of a different HPLC method for Assay and Related Impurities, a lower range for solution pH (7.6 – 8.2 versus 8.3 – 9.3 in USP monograph) and increase in the acceptance criterion for phenytoin from NMT (b) (4) % to NMT (b) (4) %. The proposed limits for pH and phenytoin are acceptable from safety perspective. However, the applicant has not provided adequate information to support the proposed HPLC method. (b) (4)

(b) (4) and the method has not been validated for determination of related substances. Therefore, accuracy of the results provided to date, including stability data cannot be assured.

Until the applicant has adequately addressed the deficiencies related to the Related Substances determination, an expiration dating period cannot be assigned to the product. Additionally, the "in-use" data provided to support compatibility of the product with IV diluents and infusions sets is inadequate. The product must be diluted prior to IV infusion and the proposed labeling lists 5% dextrose or 0.9% saline as suitable diluents. However, the applicant did not test compatibility with 5% dextrose, testing with 0.9% saline did not cover the full concentration range stated in labeling, and validation data for the assay and impurities method used in the compatibility study was not provided.

Facilities

All facilities that will be involved in commercial manufacture and testing of fosphenytoin sodium and Sesquient (fosphenytoin sodium) injection are currently acceptable.

Environmental Assessment

The applicant submitted a claim for categorical exclusion under 21 CFR § 25.31(a). Approval of the application is not expected to increase use of the active moiety, as the product would be used in place of currently approved products and there are no extraordinary circumstances. The claim is granted.

C. Special Product Quality Labeling Recommendations

Due to differences between the proposed specification and storage condition for Sesquient and the current USP monograph for Fosphenytoin Sodium Injection, labeling would need to state the differences between Sesquient and the USP monograph until the monograph is revised. This is not an approvability issue.

D. Final Risk Assessment for Sesquient (fosphenytoin sodium) Injection

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Appearance	• Formulation • Container closure • Raw materials • Process parameters • Scale • Equipment • Site	**L**	(b) (4)	Adequate	
Assay, stability		**L**		**Inadequate**	
Sterility		**H**		Adequate	
Endotoxin, pyrogen		**M**			
Fill volume		**L**		Adequate	
Osmolality		**L**		Adequate	
pH		**L**		Adequate	
Particulate matter		**M**		**Inadequate**	
Leachable/Extractables		**L**		Adequate	

E. List of Deficiencies to be Communicated

1. *The prescribing information indicates that the drug product can be diluted in either 5% dextrose or 0.9% saline to a concentration ranging from 1.5 mg PE/mL to 25 mg PE/mL.*

    a. *The compatibility study was performed at a concentration of 7.5 mg fosphenytoin sodium/mL (5 mg PE/mL) and 15 mg fosphenytoin sodium /mL (10 mg PE/mL). Provide data demonstrating that the drug product is stable at concentrations of 1.5 mg PE/mL and 25 mg PE/mL.*

    b. *The compatibility study was only performed using 0.9% sodium chloride. Provide data demonstrating that the drug product is stable in 5% dextrose. Ensure that data includes information for 1.5 mg PE/mL and 25 mg PE/mL concentrations.*

    c. *Provide a validation package for the method used to determine assay and impurities for the compatibility study.*

2. *In a response to an information request dated November 16, 2018, you indicated that the assay, identification, and impurity method was originally validated in 2007. Additionally, you stated that the method was not validated specifically for the related substances. This is not acceptable as the accuracy of the results provided to date cannot be assured. Provide data demonstrating that the method is validated ensuring that impurities remain below the proposed specifications.*

    As the impurity method has not been adequately validated at this time, the shelf-life for the drug product cannot be determined.

3. *We could not locate in-process control testing results for all manufacturing stages for your registration batches in Module 3.2.P.3.4. We recommend that you submit the results in a tabular format. If you have submitted this information earlier, please indicate its exact location.*

4. *Describe the risk mitigation strategies in your manufacturing process to control the presence of* (b) (4) *particles* (b) (4) *in the drug product.*

Additional Comment for Action Letter

This is not an approvability issues but should be addressed when the NDA is resubmitted.

As noted in our information requests from June 22, 2018, our discussion in the meeting from July 6, 2017, our response to Question 9 of the Type C Meeting dated June 3, 2016, and our response to Question 1 of the pre-IND meeting dated September 20, 2006, the proposed product does not comply with the USP Monograph for Fosphenytoin Sodium Injection. As previously advised, we encourage you to contact USP with respect to possible revisions to

the current monograph that would enable compliance for your product. Revisions are needed for acceptance criterion for both pH and phenytoin impurity limit. Please refer to the following USP website for information regarding guidelines for submitting requests for revision to the USP-NF through the pending monograph process (http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/pendingStandards/2015-06-01-pending-monograph-guideline.pdf).

Martha Heimann

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LABELING

I. Package Insert

(b) (4)

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	SESQUIENT, Fosphenytoin Injection *Reviewer's Note:* (b) (4)

Dosage form, route of administration	Injection, IV
Controlled drug substance symbol	NA
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	10 mL single-dose injection, containing 500 mg PE 2 mL single-dose injection, containing 100 mg PE *Reviewer's Note: Applicant will be asked to update PI to indicate that the (b) (4) strength contains 2 mL*

2. *Section 2 Dosage and Administration*

2 DOSAGE AND ADMINISTRATION

2.1 Important Administration Instructions to Avoid Dosing Errors

Use caution when administering TRADE NAME because of the risk of dosing errors *[see Warnings and Precautions (5.1)]*.

Phenytoin Sodium Equivalents (PE)
The dose, concentration, and infusion rate of TRADE NAME should always be expressed as phenytoin sodium equivalents (PE). There is no need to perform molecular weight-based adjustments when converting between fosphenytoin and phenytoin sodium doses. TRADE NAME should always be prescribed and dispensed in phenytoin sodium equivalent units (PE). The amount and concentration of fosphenytoin is always expressed in terms of mg of phenytoin sodium equivalents (mg PE).

Concentration of 50 mg PE/mL
Do not confuse the concentration of TRADE NAME with the total amount of drug in the vial.

Errors, including fatal overdoses, have occurred when the concentration of the vial (50 mg PE/mL) was misinterpreted to mean that the total content of the vial was 50 mg PE. These errors have resulted in two- or tenfold overdoses of TRADE NAME since each of the vials actually contains a total of 100 mg PE ((b) (4) or 500 mg PE (10 mL (b) (4). Ensure the appropriate volume of TRADE NAME is withdrawn from the vial when preparing the dose for administration. Attention to these details may prevent some TRADE NAME medication errors from occurring.

2.2 Preparation

Prior to intravenous (b) (4) infusion, dilute TRADE NAME in 5% dextrose or 0.9% saline solution for injection to a concentration ranging from 1.5 to 25 mg PE/mL. The maximum concentration of TRADE NAME in any solution should be 25 mg PE/mL. When TRADE NAME is given as an intravenous infusion, TRADE NAME needs to be diluted and should only be administered at a rate not exceeding 150 mg PE/min.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

(b) (4)

For single-dose only. After opening, any unused product should be discarded.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	(b) (4)

3. *Section 3 Dosage Forms and Strengths*

3 DOSAGE FORMS AND STRENGTHS

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Injection
Strengths: in metric system	10 mL single-dose injection, containing 500 mg PE 2 mL single-dose injection, containing 100 mg PE *Reviewer's Note: Applicant will be asked to update PI to indicate that the* (b) (4) *strength contains 2 mL*
Active moiety expression of strength with equivalence statement (if applicable)	NA
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Clear, colorless solution (b) (4) *Reviewer's Note:* (b) (4)

4. *Section 11 Description*

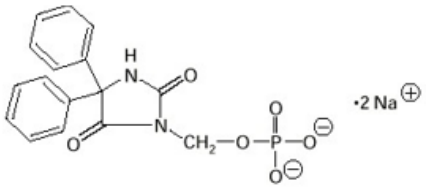
11 DESCRIPTION

(b) (4) Fosphenytoin Sodium Injection (TRADE NAME) is a prodrug intended for parenteral administration; its active metabolite is phenytoin. 1.5 mg of fosphenytoin sodium is equivalent to 1 mg phenytoin sodium, and is referred to as 1 mg phenytoin sodium equivalents (PE). The amount and concentration of fosphenytoin is always expressed in terms of mg PE.

The pharmacological class of the fosphenytoin sodium is hydantoin derivative, and the therapeutic class is anticonvulsant.

(b) (4)

The chemical name of fosphenytoin is 5,5-diphenyl-3-[(phosphonooxy)methyl]-2,4-imidazolidinedione disodium salt. The molecular structure of fosphenytoin is:



The molecular weight of fosphenytoin is 406.24.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	SESQUIENT, Fosphenytoin Injection
Dosage form and route of administration	Injection, IV
Active moiety expression of strength with equivalence statement (if applicable)	NA
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Sulfobutyl ether beta-cyclodextrin (100 mg/mL), tromethamine (2.42 mg/mL), hydrochloric acid, and sodium hydroxide *Reviewer's Note: Applicant will be asked to include the quantity of each inactive ingredient and list the inactive ingredients in alphabetical order and to refer to excipients by nonproprietary name only*
Statement of being sterile (if applicable)	Sterile
Pharmacological/ therapeutic class	Anticonvulsant
Chemical name, structural formula, molecular weight	$C_{16}H_{13}N_2Na_2O_6P$, 406.24 Da *Reviewer's Note: Applicant will be asked to include sodium after fosphenytoin as the structure and molecular weight correspond*

	to the sodium salt.
If radioactive, statement of important nuclear characteristics.	NA
Other important chemical or physical properties (such as pKa or pH)	*Reviewer's Note: Applicant will be asked to include the following statements as the drug product does not comply with the current USP monograph for fosphenytoin sodium injection label: FDA approved impurity specification for phenytoin differs from USP. FDA approved pH specification differs from USP.*

5. *Section 16 How Supplied/Storage and Handling*

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

TRADE NAME is a clear, colorless, sterile solution supplied as follows:

(b) (4)

TRADE NAME should always be prescribed in phenytoin sodium equivalents (PE) *[see Dosage and Administration (2.1) and Warnings and Precautions (5.1)]*.

1.5 mg of fosphenytoin sodium is equivalent to 1 mg phenytoin sodium, and is referred to as 1 mg PE. The amount and concentration of fosphenytoin is always expressed in terms of mg of phenytoin sodium equivalents (PE). Fosphenytoin's weight is expressed as phenytoin sodium equivalents to avoid the need to perform molecular weight-based adjustments when substituting fosphenytoin for phenytoin or vice versa.

16.2 Storage and Handling

Store TRADE NAME at room temperature. Temperature excursions are permitted between 15-30°C (59-86°F). [see USP Controlled Room Temperature]. Vials that develop particulate matter should not be used.

Injection vials are single-dose only. After opening, any unused product should be discarded.

Item	Information Provided in NDA

(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	10 mL single-dose injection, containing 500 mg PE 2 mL single-dose injection, containing 100 mg PE
Available units (e.g., bottles of 100 tablets)	10 mL and (b) (4) mL vial
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	NDC number not included
Special handling (e.g., protect from light)	After opening, any unused product should be discarded.
Storage conditions	CRT
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Emergent BioSolutions Inc

Reviewer's Assessment of Package Insert: ***Inadequate***

- Revisions identified and will be communicated to the Applicant.

II. Labels:

(b) (4)

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Present	Present
Dosage strength	Present	Present
Net contents	Present	Present
"Rx only" displayed prominently on the main panel	Present	Present
NDC number (21 CFR 207.35(b)(3)(i))	Present	Present
Lot number and expiration date (21 CFR 201.17)	Present	Present
Storage conditions	Present	Present
Bar code (21CFR 201.25)	Present	Present
Name of manufacturer/distributor	Present	Present
And others, if space is available	NA	*Reviewer's Note: Applicant will be asked to include the quantity of each inactive ingredient*

Reviewer's Assessment of Labels: ***Inadequate***

The carton/container label complies with regulatory requirements from a CMC perspective. It bears the "Rx only" statement, the NDC number, name of manufacturer, lot number, expiration date, net contents, bar code, strength, and the name (proprietary and established).

Revisions identified and will be communicated to the Applicant.

List of Deficiencies:

1. *Revise all sections to say single-dose instead of* (b) (4).
2. *Remove* (b) (4).
3. *Remove* (b) (4) *from the PI, carton labeling, and the medication guide.*
4. *In the dosage forms and strengths section, include* (b) (4)
5. *In the description section:*

a. *Include the quantity of each inactive ingredient. List the inactive ingredients in alphabetical order.*

b. *Include sodium after fosphenytoin as the structure and molecular weight correspond to the sodium salt.*

c. *Include the following statements as the drug product does not comply with the current USP monograph for fosphenytoin sodium injection label: FDA approved impurity specification for phenytoin differs from USP. FDA approved pH specification differs from USP.*

6. *Include the NDC number in the how supplied section of the physician's insert.*

7. *As part of the carton label, include the quantity of each inactive ingredient.*

Overall Assessment and Recommendation: Inadequate

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MICROBIOLOGY

Product Background:

NDA: 210864

Drug Product Name / Strength: Sesquient (Capitsol-Enabled Fosphenytoin Sodium Injection), sterile injection, 75 mg/mL, packaged as (b) (4) mg/2 mL in a (b) (4) vial and (b) (4) mg/10 mL in a 10 mL vial, single dose

Route of Administration: intravenous or intramuscular

Applicant Name: Sedor Pharmaceuticals

Manufacturing Site:
(b) (4) Emergent BioSolutions, Inc.
(b) (4)
Baltimore, MD 21230

Method of Sterilization: (b) (4)

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): **N/A**

Review Summary:

List Submissions Being Reviewed: 05/22/2018, 06/29/2018 (IR response to CMC), 07/13/2018 (IR response to CMC), 10/29/2018 (IR response to CMC/Microbiology), 12/07/2018 (IR response to CMC/Microbiology), 12/21/2018 (IR response to CMC/Microbiology), and 01/14/2019 (IR response to CMC/Microbiology)

Highlight Key Outstanding Issues from Last Cycle: N/A

Remarks: The drug product is (b) (4).

Concise Description Outstanding Issues Remaining: The applicant did not provide the commercial production (b) (4).

Supporting Documents:

- Type V DMF (b) (4) (Subject: (b) (4)

(b) (4).

- Review D (b) (4) dated 12/20/2017, on the V-drive, for the (b) (4) (adequate).

List Number of Comparability Protocols (ANDA only): N/A

S Drug Substance

Drug substance is not reviewed in this application as the final drug product is subject to (b) (4).

P.1 Description of the Composition of the Drug Product

06/29/2018 submission, Section P.1, "Description and composition of the drug product" and P.2 "Container closure system"

- **Description of drug product –** Clear, colorless, sterile solution.
- **Drug product composition –**

Ingredient	Function	Quantity/2 mL	Quantity/10 mL
Fosphenytoin Sodium	API	(b) (4)	(b) (4)
(b) (4)		(b) (4)	
Tromethamine			
Hydrochloric Acid	pH adjuster	q.s. to pH	q.s. to pH
Sodium Hydroxide	pH adjuster	q.s. to pH	q.s. to pH
WFI		(b) (4)	

- **Description of container closure system –**

	Container Closure	Description; Manufacturer
2 mL fill	Vial	(b) (4)
	Stopper	
	Seal	
10 mL fill	Vial	
	Stopper	
	Seal	

Reviewer's Assessment: ***Adequate***

The applicant provided an adequate description of the drug product and container closures.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

Container/Closure and Package Integrity

06/29/2018 submission, Section P.2, "Microbiological Attributes"

(b) (4)

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