CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204485Orig1s013

Trade Name:	VASOSTRICT
Generic or Proper Name:	vasopressin
Sponsor:	Par Sterile Products LLC
Approval Date:	April 15, 2020
Indication:	Vasostrict® is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.

CENTER FOR DRUG EVALUATION AND RESEARCH

204485Orig1s013

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	**X**
Statistical Review(s)	**X**
Microbiology / Virology Review(s)	**X**
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204485Orig1s013

APPROVAL LETTER

NDA 204485/S-013

APPROVAL LETTER

Par Sterile Products LLC
Attention: Katharine Nowalski
Manager, Regulatory Affairs
Six Ram Ridge Road
Chestnut Ridge, NY 10977

Dear Ms. Nowalski:

Please refer to your Supplemental New Drug Application (sNDA) dated and received December 20, 2019, and your amendments, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Vasostrict (vasopressin injection).

This Prior Approval supplemental new drug application provides for the addition of 40 units/100 mL and 60 units/100 mL single dose vial presentations.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm. Content of labeling must be identical to the enclosed labeling (text for the prescribing information) with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eLIST may be found in the guidance for industry titled *SPL Standard for Content of Labeling Technical Qs and As* at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format,

that includes the changes approved in this supplemental application, as well as annual reportable changes, and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (May 2015, Revision 3)*. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved NDA 204485/S-013.**" Approval of this submission by FDA is not required before the labeling is used.

We remind you that you must comply with reporting requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Abolade (Bola) Adeolu, Regulatory Business Process Manager, at (301) 796 - 4264.

Sincerely,

{See appended electronic signature page}

Ramesh Raghavachari, PhD
Chief, Branch I
Division of Post-Marketing Activities I
Office of Lifecycle Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosures:
Content of Labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204485Orig1s013

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use VASOSTRICT® safely and effectively. See full prescribing information for VASOSTRICT®.

VASOSTRICT® (vasopressin injection) for intravenous use
Initial U.S. Approval: 2014

----------RECENT MAJOR CHANGES----------

Contraindications (4)	05/2019
Warnings and Precautions (5.2)	02/2020

----------INDICATIONS AND USAGE----------

- Vasostrict® is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines. (1)

----------DOSAGE AND ADMINISTRATION----------

- Dilute 20 units/mL single dose vial or 200 units/10 mL (20 units/mL) multiple dose vial contents with normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) to either 0.1 units/mL or 1 unit/mL for intravenous administration. Discard unused diluted solution after 18 hours at room temperature or 24 hours under refrigeration. (2.1)
- The 40 units/100 mL and 60 units/100 mL single dose vials do not require further dilution prior to administration. (2.1)
- Post-cardiotomy shock: 0.03 to 0.1 units/minute (2.2)
- Septic shock: 0.01 to 0.07 units/minute (2.2)

----------DOSAGE FORMS AND STRENGTHS----------

- Injection: 20 units/mL in a single dose vial and 200 units/10 mL (20 units/mL) in a multiple dose vial. To be used after dilution. (3)
  40 units/100 mL (0.4 units/mL) and 60 units/100 mL (0.6 units/mL) in single dose vials. Ready to use. (3)

----------CONTRAINDICATIONS----------

- Vasostrict® 10 mL multiple dose vial is contraindicated in patients with known allergy or hypersensitivity to 8-L-arginine vasopressin or chlorobutanol. The 1 mL single dose vial does not contain chlorobutanol and is therefore contraindicated only in patients with a known allergy or hypersensitivity to 8-L-arginine vasopressin. (4)

----------WARNINGS AND PRECAUTIONS----------

- Can worsen cardiac function. (5.1)

----------ADVERSE REACTIONS----------

The most common adverse reactions include decreased cardiac output, bradycardia, tachyarrhythmias, hyponatremia and ischemia (coronary, mesenteric, skin, digital). (6)

To report SUSPECTED ADVERSE REACTIONS, contact Par Pharmaceutical at 1-800-828-9393 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Pressor effects of catecholamines and Vasostrict® are expected to be additive. (7.1)
- Indomethacin may prolong effects of Vasostrict®. (7.2)
- Co-administration of ganglionic blockers or drugs causing SIADH may increase the pressor response. (7.3, 7.5)
- Co-administration of drugs causing diabetes insipidus may decrease the pressor response. (7.6)

----------USE IN SPECIFIC POPULATIONS----------

- **Pregnancy:** May induce uterine contractions. (8.1)
- **Pediatric Use:** Safety and effectiveness have not been established. (8.4)
- **Geriatric Use:** No safety issues have been identified in older patients. (8.5)

Revised: 04/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Vasostrict® is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.

2 DOSAGE AND ADMINISTRATION

2.1 Preparation of Solution

Inspect parenteral drug products for particulate matter and discoloration prior to use, whenever solution and container permit.

Vasostrict® Solution for Dilution, 20 units/mL and 200 units/10 mL (20 units/mL)

Dilute Vasostrict® in normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) prior to use for intravenous administration. Discard unused diluted solution after 18 hours at room temperature or 24 hours under refrigeration.

Table 1 Preparation of diluted solutions

Fluid restriction?	Final concentration	Mix	
		Vasostrict®	Diluent
No	0.1 units/mL	2.5 mL (50 units)	500 mL
Yes	1 unit/mL	5 mL (100 units)	100 mL

Vasostrict® Premixed Solution, 40 units/100 mL (0.4 units/mL) and 60 units/100 mL (0.6 units/mL)

This product does not require further dilution prior to administration.

2.2 Administration

The goal of treatment is optimization of perfusion to critical organs, but aggressive treatment can compromise perfusion of organs, like the gastrointestinal tract, whose function is difficult to monitor. The following advice is empirical. In general, titrate to the lowest dose compatible with a clinically acceptable response.

For post-cardiotomy shock, start with a dose of 0.03 units/minute. For septic shock, start with a dose of 0.01 units/minute. If the target blood pressure response is not achieved, titrate up by 0.005 units/minute at 10- to 15-minute intervals. The maximum dose for post-cardiotomy shock is 0.1 units/minute and for septic shock 0.07 units/minute. After target blood pressure has been maintained for 8 hours without the use of catecholamines, taper Vasostrict® by 0.005 units/minute every hour as tolerated to maintain target blood pressure.

3 DOSAGE FORMS AND STRENGTHS

Vasostrict® (vasopressin injection, USP) is a clear, practically colorless solution for intravenous administration available as 20 units/mL in a single dose vial and 200 units/10 mL (20 units/mL) in a multiple dose vial. To be used after dilution.

Vasostrict® is also available premixed as 40 units/100 mL (0.4 units/mL) and 60 units/100 mL (0.6 units/mL) in single dose vials. Ready to use.

4 CONTRAINDICATIONS

Vasostrict® 10 mL multiple dose vial is contraindicated in patients with known allergy or hypersensitivity to 8-L-arginine vasopressin or chlorobutanol. The 1 mL single dose vial does not contain chlorobutanol and is therefore contraindicated only in patients with a known allergy or hypersensitivity to 8-L-arginine vasopressin.

5 WARNINGS AND PRECAUTIONS

5.1 Worsening Cardiac Function

Use in patients with impaired cardiac response may worsen cardiac output.

5.2 Reversible Diabetes Insipidus

Patients may experience reversible diabetes insipidus, manifested by the development of polyuria, a dilute urine, and hypernatremia, after cessation of treatment with vasopressin. Monitor serum electrolytes, fluid status and urine output after vasopressin discontinuation. Some patients may require readministration of vasopressin or administration of desmopressin to correct fluid and electrolyte shifts.

6 ADVERSE REACTIONS

The following adverse reactions associated with the use of vasopressin were identified in the literature. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

Bleeding/lymphatic system disorders: Hemorrhagic shock, decreased platelets, intractable bleeding

Cardiac disorders: Right heart failure, atrial fibrillation, bradycardia, myocardial ischemia

Gastrointestinal disorders: Mesenteric ischemia

Hepatobiliary: Increased bilirubin levels

Renal/urinary disorders: Acute renal insufficiency

Vascular disorders: Distal limb ischemia

Metabolic: Hyponatremia

Skin: Ischemic lesions

Postmarketing Experience

Reversible diabetes insipidus *[see Warnings and Precautions (5.2)]*

7 DRUG INTERACTIONS

7.1 Catecholamines

Use with *catecholamines* is expected to result in an additive effect on mean arterial blood pressure and other hemodynamic parameters.

7.2 Indomethacin

Use with *indomethacin* may prolong the effect of Vasostrict® on cardiac index and systemic vascular resistance *[see Clinical Pharmacology (12.3)]*.

7.3 Ganglionic Blocking Agents

Use with *ganglionic blocking agents* may increase the effect of Vasostrict® on mean arterial blood pressure *[see Clinical Pharmacology (12.3)]*.

7.4 Furosemide

Use with *furosemide* increases the effect of Vasostrict® on osmolar clearance and urine flow *[see Clinical Pharmacology (12.3)]*.

7.5 Drugs Suspected of Causing SIADH

Use with *drugs suspected of causing SIADH* (e.g., SSRIs, tricyclic antidepressants, haloperidol, chlorpropamide, enalapril, methyldopa, pentamidine, vincristine, cyclophosphamide, ifosfamide, felbamate) may increase the pressor effect in addition to the antidiuretic effect of Vasostrict®.

7.6 Drugs Suspected of Causing Diabetes Insipidus

Use with *drugs suspected of causing diabetes insipidus* (e.g., demeclocycline, lithium, foscarnet, clozapine) may decrease the pressor effect in addition to the antidiuretic effect of Vasostrict®. Hemodynamic monitoring is recommended; adjust the dose of vasopressin as needed.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Risk Summary: There are no adequate or well-controlled studies of Vasostrict® in pregnant women. It is not known whether vasopressin can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Animal reproduction studies have not been conducted with vasopressin *[see Clinical Pharmacology (12.3)]*.

Clinical Considerations: Because of increased clearance of vasopressin in the second and third trimester, the dose of Vasostrict® may need to be up-titrated to doses exceeding 0.1 units/minute in post-cardiotomy shock and 0.07 units/minute in septic shock.

Vasostrict® may produce tonic uterine contractions that could threaten the continuation of pregnancy.

8.3 Nursing Mothers

It is not known whether vasopressin is present in human milk. However, oral absorption by a nursing infant is unlikely because vasopressin is rapidly destroyed in the gastrointestinal tract. Consider advising a lactating woman to pump and discard breast milk for 1.5 hours after receiving vasopressin to minimize potential exposure to the breastfed infant.

8.4 Pediatric Use

Safety and effectiveness of Vasostrict® in pediatric patients with vasodilatory shock have not been established.

8.5 Geriatric Use

Clinical studies of vasopressin did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy *[see Warnings and Precautions (5), Adverse Reactions (6), and Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Overdosage with Vasostrict® can be expected to manifest as consequences of vasoconstriction of various vascular beds (peripheral, mesenteric, and coronary) and as hyponatremia. In addition, overdosage may lead less commonly to ventricular tachyarrhythmias (including Torsade de Pointes), rhabdomyolysis, and non-specific gastrointestinal symptoms.

Direct effects will resolve within minutes of withdrawal of treatment.

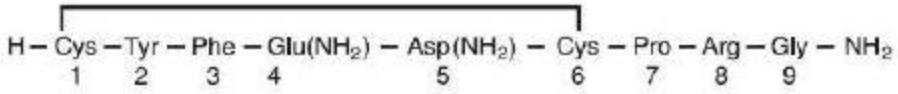
11 DESCRIPTION

Vasopressin is a polypeptide hormone that causes contraction of vascular and other smooth muscles and antidiuresis. Vasostrict® is a sterile, aqueous solution of synthetic arginine vasopressin for intravenous administration.

The 1 mL solution contains vasopressin 20 units/mL, Water for Injection, USP, and sodium acetate buffer adjusted to a pH of 3.8. The 10 mL solution contains vasopressin 20 units/mL, chlorobutanol, NF 0.5% as a preservative, Water for Injection, USP and sodium acetate buffer adjusted to a pH of 3.8.

The 100 mL solution contains vasopressin 0.4 units/mL or 0.6 units/mL. Each mL of the 0.4 unit/mL strength also contains dextrose anhydrous, acetic acid, sodium acetate and Water for Injection, USP. Each mL of the 0.6 unit/mL strength also contains dextrose anhydrous, acetic acid, sodium acetate and Water for Injection, USP. Sodium hydroxide and hydrochloric acid are included to adjust to a pH of 3.8.

The chemical name of vasopressin is Cyclo (1-6) L-Cysteinyl-L-Tyrosyl-L-Phenylalanyl-L-Glutaminyl-L-Asparaginyl-L-Cysteinyl-L-Prolyl-L-Arginyl-L-Glycinamide. It is a white to off-white amorphous powder, freely soluble in water. The structural formula is:



Molecular Formula: $C_{46}H_{65}N_{15}O_{12}S_2$ Molecular Weight: 1084.23

One mg is equivalent to 530 units.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The vasoconstrictive effects of vasopressin are mediated by vascular V_1 receptors. Vascular V_1 receptors are directly coupled to phopholipase C, resulting in release of calcium, leading to vasoconstriction. In addition, vasopressin stimulates antidiuresis via stimulation of V_2 receptors which are coupled to adenyl cyclase.

12.2 Pharmacodynamics

At therapeutic doses exogenous vasopressin elicits a vasoconstrictive effect in most vascular beds including the splanchnic, renal and cutaneous circulation. In addition, vasopressin at pressor doses triggers contractions of smooth muscles in the gastrointestinal tract mediated by muscular V_1-receptors and release of prolactin and ACTH via V_3 receptors. At lower concentrations typical for the antidiuretic hormone vasopressin inhibits water diuresis via renal V_2 receptors.

In patients with vasodilatory shock vasopressin in therapeutic doses increases systemic vascular resistance and mean arterial blood pressure and reduces the dose requirements for norepinephrine. Vasopressin tends to decrease heart rate and cardiac output. The pressor effect is proportional to the infusion rate of exogenous vasopressin. Onset of the pressor effect of vasopressin is rapid, and the peak effect occurs within 15 minutes. After stopping the infusion the pressor effect fades within 20 minutes. There is no evidence for tachyphylaxis or tolerance to the pressor effect of vasopressin in patients.

12.3 Pharmacokinetics

At infusion rates used in vasodilatory shock (0.01-0.1 units/minute) the clearance of vasopressin is 9 to 25 mL/min/kg in patients with vasodilatory shock. The apparent $t_{1/2}$ of vasopressin at these levels is $\leq$ 10 minutes. Vasopressin is predominantly metabolized and only about 6% of the dose is excreted unchanged in urine. Animal experiments suggest that the metabolism of vasopressin is primarily by liver and kidney. Serine protease, carboxipeptidase and disulfide oxido-reductase cleave vasopressin at sites relevant for the pharmacological activity of the hormone. Thus, the generated metabolites are not expected to retain important pharmacological activity.

Drug-Drug Interactions

Indomethacin more than doubles the time to offset for vasopressin's effect on peripheral vascular resistance and cardiac output in healthy subjects *[see Drug Interactions (7.2)]*.

The ganglionic blocking agent tetra-ethylammonium increases the pressor effect of vasopressin by 20% in healthy subjects *[see Drug Interactions (7.3)]*.

Furosemide increases osmolar clearance 4-fold and urine flow 9-fold when co-administered with exogenous vasopressin in healthy subjects *[see Drug Interactions (7.4)]*.

Halothane, morphine, fentanyl, alfentanyl and sufentanyl do not impact exposure to endogenous vasopressin.

Specific Populations

Pregnancy: Because of a spillover into blood of placental vasopressinase the clearance of exogenous and endogenous vasopressin increases gradually over the course of a pregnancy. During the first trimester of pregnancy the clearance is only slightly increased. However, by the third trimester the clearance of vasopressin is increased about 4-fold and at term up to 5-fold. After delivery the clearance of vasopressin returns to pre-conception baseline within two weeks.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No formal carcinogenicity or fertility studies with vasopressin have been conducted in animals. Vasopressin was found to be negative in the *in vitro* bacterial mutagenicity (Ames) test and the *in vitro* Chinese hamster ovary (CHO) cell chromosome aberration test. In mice, vasopressin has been reported to have an effect on function and fertilizing ability of spermatozoa.

14 CLINICAL STUDIES

Increases in systolic and mean blood pressure following administration of vasopressin were observed in 7 studies in septic shock and 8 in post-cardiotomy vasodilatory shock.

16 HOW SUPPLIED/STORAGE AND HANDLING

Vasostrict® (vasopressin injection, USP) is a clear, practically colorless solution for intravenous administration available as:

NDC 42023-164-25: A carton of 25 single dose vials. Each vial contains vasopressin 1 mL at 20 units/mL.

NDC 42023-190-01: A carton of 1 multiple dose vial. Each vial contains vasopressin 10 mL at 200 units/10 mL (20 units/mL).

NDC 42023-219-10: A carton of 10 single dose vials. Each vial contains vasopressin 100 mL at 40 units/100 mL (0.4 units/mL).

NDC 42023-220-10: A carton of 10 single dose vials. Each vial contains vasopressin 100 mL at 60 units/100 mL (0.6 units/mL).

Store between 2°C and 8°C (36°F and 46°F). Do not freeze.

Vials may be held up to 12 months upon removal from refrigeration to room temperature storage conditions (20°C to 25°C [68°F to 77°F], USP Controlled Room Temperature), anytime within the labeled shelf life. Once removed from refrigeration, unopened vial should be marked to indicate the revised 12 month expiration date. If the manufacturer's original expiration date is shorter than the revised expiration date, then the shorter date must be used. Do not use Vasostrict® beyond the manufacturer's expiration date stamped on the vial.

After initial entry into the 10 mL vial, the remaining contents must be refrigerated. Discard the refrigerated 10 mL vial after 30 days after first puncture.

The storage conditions and expiration periods are summarized in the following table.

	Unopened Refrigerated 2°C to 8°C (36°F to 46°F)	Unopened Room Temperature 20°C to 25°C (68°F to 77°F) Do not store above 25°C (77°F)	Opened (After First Puncture)
1 mL Vial	Until manufacturer expiration date	12 months or until manufacturer expiration date, whichever is earlier	N/A
10 mL Vial	Until manufacturer expiration date	12 months or until manufacturer expiration date, whichever is earlier	30 days
100 mL Vial	Until manufacturer expiration date	12 months or until manufacturer expiration date, whichever is earlier	N/A

Distributed by:
Par Pharmaceutical
Chestnut Ridge, NY 10977

R03/20 OS164J-01-90-XX

Vasostrict® is a registered trademark of Par Pharmaceutical Companies, Inc.

PULL

NDC 42023-**220**-01

Rx only

Vasostrict®
(Vasopressin Injection, USP)
60 Units per 100 mL
(0.6 units per mL)

For Intravenous Infusion
Ready to Use
100 mL Single Dose Vial

PAR PHARMACEUTICAL

Dosage: See full prescribing information.

Store between 2°C and 8°C (36°F and 46°F). Vials may be held at 20°C to 25°C (68°F to 77°F) for up to 12 months.

Avoid freezing.

103/2020 LA220J-52-90-01

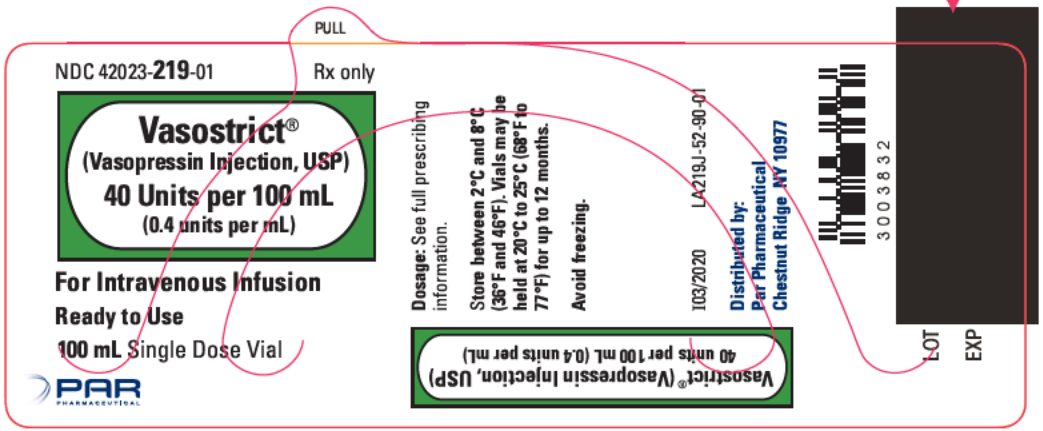
Distributed by:
Par Pharmaceutical
Chestnut Ridge, NY 10977

3003830

LOT

EXP

Vasostrict® (Vasopressin Injection, USP)
60 units per 100 mL (0.6 units per mL)

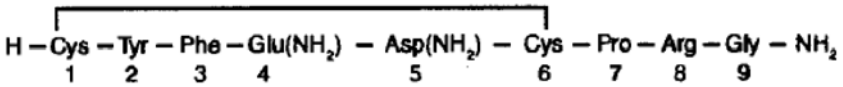

PULL
NDC 42023-219-01
Rx only
Vasostrict®
(Vasopressin Injection, USP)
40 Units per 100 mL
(0.4 units per mL)
For Intravenous Infusion
Ready to Use
100 mL Single Dose Vial
PAR PHARMACEUTICAL
Dosage: See full prescribing information.
Store between 2°C and 8°C (36°F and 46°F). Vials may be held at 20°C to 25°C (68°F to 77°F) for up to 12 months.
Avoid freezing.
LA219J-52-90-01
103/2020
Distributed by:
Par Pharmaceutical
Chestnut Ridge, NY 10977
300383 2
LOT
EXP
Vasostrict® (Vasopressin Injection, USP)
40 units per 100 mL (0.4 units per mL)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204485Orig1s013

CHEMISTRY REVIEW(S)

CMC REVIEW:	1. ORGANIZATION:	2. NDA Number: 204-485
3. Name and Address of Applicant (City & State): Par Sterile Products, LLC 6 Ram Ridge Road Chestnut Ridge, New York 10977		**4. Supplement(s):** **Number(s) Date(s)** S-013 12/20/2019
5. Drug Name: Vasostrict®	**6. Nonproprietary Name:** Vasopressin	**7. Amendments: - Dates**
8. Supplement Provides For: addition of 40 units/100 mL and 60 units/100 mL single dose presentations.		
1. Pharmacological Category: To increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.	**10. How Dispensed:** Rx	**11. Related NDAs/DMFs:**
12. Dosage Form(s): Injection	**13. Potency:** 40 units/100 mL and 60 units/100 mL	
14. Chemical Name and Structure: Cyclo (1-6) L-Cysteinyl-L-Tyrosyl-L-Phenylalanyl-L-Glutaminyl-L-Asparaginyl-L-Cysteinyl-L-Prolyl-L-Arginyl-L-Glycinamide.  Molecular Formula: $C_{46}H_{65}N_{15}O_{12}S_2$ Molecular weight: 1084.23 One mg is equivalent to 530 units		**15. Records/Reports:** **Current** **Yes X No** **Reviewed** **Yes No X**

16. Comments: The **PAS** proposes to add two single-dose presentations (40 units/100 mL and 60 units/100 mL) for immediate use without further the need for further dilution. The applicant submitted the complete set of CMC information to support the proposed changes. The applicant submitted the batch analysis and stability results for seven batches of drug product, including 4 batches for the 40 units/100 mL presentation (12 months under 25ºC/60% RH and 18 months under refrigeration for three batches and three months stability data under both conditions for one batch) and 3 batches for the 60 units/100 mL (12 months under 25ºC/60% RH and 18 months under refrigeration). 24-month and 12-month shelf lives are proposed for refrigeration and controlled room temperature respectively. The extractables and leachables study results and the risk assessment for elemental impurities are submitted under 3.2.P.2.

This supplement is the subject of micro review for the proposed change.

Micro was reviewed by David Bateman, Ph.D., dated 4/10/2020 and found **adequate** for approval on the basis of sterility assurance due to deficiencies.

Biopharmaceutics was reviewed by Huong Moldthan, Ph.D., dated 3/24//2020 and **recommend approval** from a Biopharmaceutics perspective.

The extractable and leachable (E&L) study performed by the applicant was reviewed by **PharmTox** reviewer Rama Dwivedi, Ph.D., dated 3/12/2020. According to the PharmTox reviewer, the results of the E&L study the Vasostrict® Pre-mix for injection, suggest the exposure of the target compounds migrating from the container closure system is lower than their respective ADE/PDEs and ***considered to be safe for human use.***

Statistical analysis of the proposed 24-month refrigerated (2-8°C) shelf life with 12 months of time out of refrigeration at controlled room temperature (25°C) was evaluated by Stat reviewer XIAOYU CAI, Ph.D., dated 3/9/2020. According to the Stat Reviewer, t*he data supported by the statistical analysis on the Out of Refrigeration (**OOR**) Study.*		
17. Conclusions and Recommendations: The supplement is **approved**.		
18. Reviewer:		
Name: Kris Raman, Ph.D. Sr. CMC Reviewer	**Signature:**	**Date Completed:** 3/31/2020, updated 4/10/2020

CMC REVIEW NOTES

This **PA** supplement provides for a 40 units/100 mL and 60 units/100 mL single dose vial presentations for the same indication, route of administration and dosage form as our current approved Vasostrict® presentations. The proposed single dose presentations will allow for immediate use of the finished product without the need for further dilution prior to administration (premixed). The differences between the current approved and proposed products are outlined in the table below.

Conditions	Approved – Vasostrict Presentations		Proposed – Vasostrict Premixed Presentations	
Strength	20 units/mL	200 units/10 mL	40 units/100 mL	60 units/100 mL
Dosage Form	Injection	Injection	Injection	Injection
Route of Administration	Intravenous	Intravenous	Intravenous	Intravenous
Active (vasopressin)	20 units/mL	20 units/mL	0.4 units/mL	0.6 units/mL
Excipients	• Sodium Acetate (buffering agent) (b) (4) • Water for Injection	• Chlorobutanol (preservative) • Sodium Acetate (buffering agent) (b) (4) • Water for Injection	• Dextrose Anhydrous (b) (4) • Acetic Acid (b) (4) • Sodium Acetate (b) (4) • Sodium Hydroxide* • Hydrochloric Acid* • Water for Injection	• Dextrose Anhydrous (b) (4) • Acetic Acid (b) (4) • Sodium Acetate (b) (4) • Sodium Hydroxide* • Hydrochloric Acid* • Water for Injection
Container Configuration	1 mL glass vial	10 mL glass vial	100 mL glass vial	100 mL glass vial

*pH adjustment

Vasostrict® 40 units/100 mL and 60 units/100 mL vials will be produced at the same manufacturing facility as the 1 mL and 10 mL vial presentation (Rochester, MI).

As part of the supplement, additional outside testing laboratories were added to the application to support the testing of the proposed Vasostrict® 40 units/100 mL and 60 units/100 mL formulations. Refer to Section 3.2.P.3.1 and Section 1.3.3 for additional information.

DRUG SUBSTANCE:

The active pharmaceutical ingredient (**API**) has not changed from that which is currently approved under NDA 204-485.

Control of Drug Substance:

Specification:

The drug substance specifications for vasopressin have not changed from those which are currently approved.

Batch Analysis:

Krishna Raman

Digitally signed by Krishna Raman
Date: 4/10/2020 02:49:36PM
GUID: 508da7210002a0a804126eedcec07751

Ramesh Raghavachari

Digitally signed by Ramesh Raghavachari
Date: 4/10/2020 05:04:29PM
GUID: 502d0913000029f375128b0de8c50020

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204485Orig1s013

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Division of Cardiovascular and Renal Products

Date: March 12, 2020
From: Rama Dwivedi, Ph.D.
Pharmacologist

Through: Xuan Chi, MD, PhD.
Pharm/Tox Team Leader (Acting)

Norman Stockbridge, M.D., Ph.D.
Division Director, Cardiovascular and Renal Products (DCRP)

To: Office of Pharmaceutical Quality (OPQ)

Subject: Consult Request

Date:	12/20/2019
Application:	NDA -204485/S-013
Drug Product:	Vasostrict
Applicant:	Par Sterile Products LLC

Background Information

The Vasostrict® (vasopressin injection, USP) manufactured by Par Sterile Products, LLC was approved on April 17, 2014 for the treatment of vasodilatory shock, including post-cardiotomy shock and septic shock in pursuant to Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The Par Sterile Products submitted supplement (eCTD Sequence #: 0083/Supplement S-013) on December 20, 2019 for the approval of a 40 units/100 mL and a 60 units/100 mL single dose vial presentations (same indication, route of administration and dosage form as approved Vasostrict® presentations) for immediate use of the finished product without the need for further dilution prior to administration (premixed). The active pharmaceutical ingredient (API) has not been changed from the referenced drug product (NDA 204485). The Vasostrict® Pre-mix for injection is marketed in two presentations of either 0.4 units/mL or 0.6 units/mL in a 100 mL stoppered glass vial.

In addition, Sponsor also submitted extractables and leachable (E&L) studies conducted toward the assessment of the potential E & L materials from the Vasostrict® Pre-mix Drug Product (b) (4) (b) (4) used in the production of Vasostrict® Pre-mix for injection. This consult is being requested from OPQ to assess and evaluate that E & L in drug products (as impurities) from the (b) (4) used in the production of Vasostrict® Pre-mix for injection. The data submitted from two E&L studies is reviewed below.

Review of the Study Reports

PD/EL/Assessment/Extractables and Leachable Risk Assessment for Vasostrict Pre-Mix for Injection (b) (4)

Report Number: PAR-(b) (4)-01455 (b) (4)-18162.02
Conducting Lab: (b) (4)
Sponsor: Par Sterile Products LLC.
Final Report: November 01, 2019

Purpose

Assessment of the Vasostrict® Pre-mix for injection (b) (4) to evaluate the extractables and leachables (E&L) profile of the drug product.

Methods

The Vasostrict® Pre-mix for injection with active pharmaceutical ingredient (API) Arginine Vasopressin, USP, is marketed either as 0.4 units/mL or 0.6 units/mL preparations in a 100 mL stoppered glass. Vasostrict® Pre-mix formulation is given below.

Component	Concentration
Vasopressin (API)	0.4 or 0.6 units/mL
Dextrose, Anhydrous	(b) (4)
Acetic Acid (b) (4)	
Sodium Hydroxide (b) (4)	
Sodium Acetate (b) (4)	
Hydrochloric Acid (b) (4)	
WFI	

Review of this E&L risk assessment is based on the information provided by the Sponsor concerning the materials of construction, equipment, the actual conditions of use in the manufacturing of Vasostrict® Pre-mix and review of the Par's extractables test data. In order to identify potential extractable compounds, present in Vasostrict® Pre-mix for Injection Drug Product (b) (4) this assessment considered the (b) (4) (b) (4), and cover the information provided by the following documents:

- Data provided by Par Pharmaceuticals
- Vasostrict® Pre-mix for Injection (b) (4)
- Par Engineering Study PES Number 2017-011
- (b) (4)
- Websites for the equipment vendors
- Toxicological Assessment of Impurities in Vasostrict Drug Product

The E&L risk evaluation of the components in the Vasostrict® Pre-mix for injection processing (b) (4) considered the (b) (4) when applicable.

Vasostrict® Pre-mix for Injection Processing (b) (4)

(b) (4)

(b) (4)

3 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

Conclusion

The results of the E&L study performed for the processing components used in the Vasostrict® Pre-mix for injection production, suggest the levels of the target compounds ((b) (4) (b) (4) migrating from the (b) (4) are below the thresholds of toxicologic concern levels. The exposure to (b) (4) is evel.

PD/EL/Assessment/Strategy for Evaluating the Extractables and Leachables Risk for the Vasostrict Pre-Mix Solution for Injection Container Closure System

Report Number: PAR-(b) (4)-01456/(b) (4)18153.02
Conducting Lab: (b) (4)
Sponsor: Par Sterile Products LLC.
Final Report: November 01, 2019

Purpose

Assessment of the Vasostrict® Pre-mix for injection container closure system to evaluate the extractables and leachables (E&L) profile of the drug product.

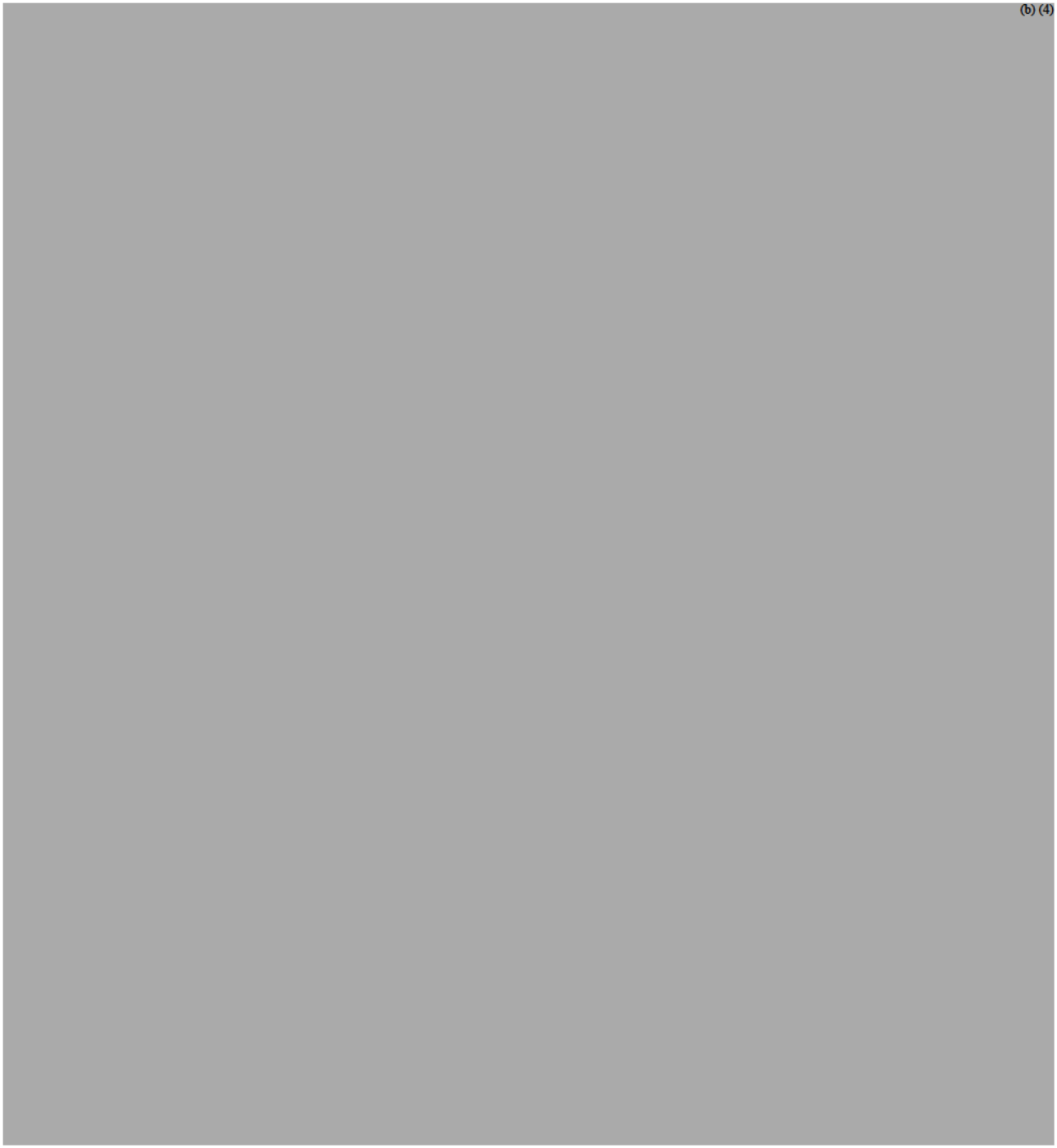
Methods

The Vasostrict® Pre-mix formulation for injection with active pharmaceutical ingredient (API) Arginine Vasopressin, USP, is marketed either as 0.4 units/mL or 0.6 units/mL and packaged in a container closure system consisting of a 100 mL vial and (b) (4) stopper with (b) (4) cap as below:

Vasostrict® Pre-mix for Injection CCS Components

Component	Vendor	Part Number	Par Item Number	Material
100 mL, (b) (4) Vial	(b) (4)			
(b) (4) Stopper				
(b) (4) Cap				

(b) (4)



Conclusion and Discussion

Toxicology Assessment of extractable impurities in Vasostrict Drug Product determined that the maximum dose of the leachable [redacted] from the Vasostrict® Pre-mix drug product for Injection would be less than or equal to [redacted] and [redacted] will be [redacted] The permitted daily exposure (PDE) for [redacted] is [redacted] (per ICH-Q3C). For [redacted] the sponsor proposed a PDE level of [redacted] based on published literature ([redacted] As per Sponsor's evaluation, [redacted] is not genotoxic, [redacted] has

13 Page(s) have been Withheld in Full as b4 (TS/CS) immediately following this page

agreed on a TTC level of [redacted] based on [redacted]. Therefore, the reviewing pharmacologist disagree with the Sponsor's PDE level for [redacted] and recommended a level of [redacted]. The maximum dosing of the most dilute presentation of this drug product is [redacted] per day.

Based on the PDEs of [redacted] and [redacted] the values of leached product are [redacted]-fold and [redacted] fold lower than their respective ADE/PDEs. The leachable exposure to [redacted] is calculated to be [redacted], lower than the SCT level of [redacted] for any leachables in IV or SC products. Thus, there is no risk anticipated as adverse health effects from the presence of these leachable impurities present in Vasostrict® Pre-mix for Injection as proposed by the Sponsor.

Recommendations

The results of the E&L study performed by the Sponsor for the Vasostrict® Pre-mix for injection, suggest the exposure of the target compounds migrating from the container closure system is lower than their respective ADE/PDEs and considered to be safe for human use.

References

1. [redacted]
2.
3.
4.
5.
6.
7.

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/

RAMA S DWIVEDI
03/12/2020 11:22:35 AM

XUAN CHI
03/12/2020 11:26:18 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204485Orig1s013

STATISTICAL REVIEW(S)

US Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

Biometrics Division: VI

NDA NO.:	204485
SERIAL NO.:	S013
DATE RECEIVED BY OB:	1/8/2020
DRUG NAME:	Vasostrict
SPONSOR:	Par Sterile Products, LLC
INDICATION:	To increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.
DOSAGE FORM:	Injection
STRENGTHS:	0.4U/mL, 0.6U/mL
REVIEW FINISHED DATE:	03/06/2020
CMC STATISTICAL REVIEWER:	Xiaoyu Cai, Ph.D
NAME OF REQUESTOR:	Kris P Raman, Ph.D / OPQ

Secondary Reviewer:
Meiyu Shen, Ph.D., Team Leader, Mathematical Statistician, CDER/OTS/OB/DB VI

Concur:
Yi Tsong, Ph.D., Division Director, DBVI, CDER/OTS/OB/DB VI

Distribution: NDA 204485
CDER/OTS/OB/DBVI/ Yi Tsong
CDER/OTS/OB/DBVI/ Meiyu Shen
CDER/OTS/OB/DBVI/ Atiar Mohammad Rahman
CDER/OPQ/OLDP/DPMAI/PMB1/Kris P Raman
CDER/OPQ/OPRO/DRBPMII/RBPMB4/Abolade Adeolu

Table of Contents

List of Tables

List of Figures

1. Executive Summary

PAR Pharmaceutical (the Applicant) submitted a Prior Approval Supplement (PAS) to FDA (the Agency) on Dec. 20, 2019 to seek approval of 0.4U/mL and 0.6U/mL single dose vial presentations (strength) for the same indication, route of administration and dosage form as their current approved Vasostrict® presentations. This review provides the stability evaluation on stability-indicating attributes for Vasostrict for the two new strengths 0.4U/mL and 0.6U/mL with two orientations Inverted and Upright. The statistical reviewers are requested to determine if the Applicant's proposed 24-month refrigerated (2-8°C) shelf life with 12 months of time out of refrigeration at controlled room temperature (25°C) are supported by the applicant's provided stability study data.

Among the three studies submitted by the Applicant summarized in **Table 3**, the Out of Refrigeration (OOR) study which transfer the sample to 25°C for 12 months after stored at 5°C for 12 months gives the worst condition for the shelf life proposed by the Applicant. Our analysis will be focusing on analyzing whether the 12 months OOR study data of sample at 25°C (after stored at 5°C for 12 months) and its corresponded 95% confidence limits are within the specifications for the Applicant's proposed shelf life. More specifically, the proposed shelf life is acceptable if the 12 months OOR study data (and its 95% confidence limit) are within the stability specifications provided in **Table 2** for all ten attributes, both strengths and both orientations.

The applicant initially provided 6 months of sample stored at 25°C after stored at 5°C for 12 months for the OOR study, and then submitted the 9 months and 12 months of OOR study data upon the Information Request sent out by the FDA statistical reviewers and CMC reviewer on Feb. 14, 2020.

Based on my independent analysis on the provided OOR study data, our conclusions are summarized in **Table 1** and below:

- a 24-month refrigerated (2-8°C) shelf life with 12 months of time out of refrigeration at controlled room temperature (25°C) are supported by the statistical analysis on the OOR Study data;

The detailed analyses are provided in Section 3.

Table 1: Summarized Statistical Analyses Results for OOR Study Data

Strength	Orientation	Attribute	P-slop	P-intercept	Statistical Model	Confidence Limit at the end of OOR Study***		Pass?
						Lower	Upper	
Vasostrict 0.4U/mL	Inverted	pH	NN*	NN*	No trend	NN*	NN*	Yes
		Assay	0 193	NN**	Separated slop, separated intercept	92 872	95 579	Yes
		(b) (4)						Yes
								Yes
								Yes
								Yes
								Yes
		Total-Impurities					(b) (4)	Yes
		Particulate Matter(≥10µm)	NN*	NN*	No trend	NN*	NN*	Yes
		Particulate Matter(≥25µm)	NN*	NN*	No trend	NN*	NN*	Yes
	Upright	pH	NN*	NN*	No trend	NN*	NN*	Yes
		Assay	0 898	0 231	Pooled slop, separated intercept	92 937	95 191	Yes
		(b) (4)						Yes
								Yes
								Yes
								Yes
								Yes
		Total-Impurities					(b) (4)	Yes
		Particulate Matter(≥10µm)	NN*	NN*	No trend	NN*	NN*	Yes
		Particulate Matter(≥25µm)	NN*	NN*	No trend	NN*	NN*	Yes
Vasostrict 0.6U/mL	Inverted	pH	NN*	NN*	No trend	NN*	NN*	Yes
		Assay	0 008	NN**	Separated slop, separated intercept	92 156	94 954	Yes
		(b) (4)						Yes
								Yes
								Yes
								Yes
								Yes
		Total-Impurities					(b) (4)	Yes
		Particulate Matter(≥10µm)	NN*	NN*	No trend	NN*	NN*	Yes
		Particulate Matter(≥25µm)	NN*	NN*	No trend	NN*	NN*	Yes

	Upright	pH	NN*	NN*	No trend	NN*	NN*	Yes
		Assay	0 294	0 002	Pooled slop, separated intercept	91 705	95 347	Yes
							(b) (4)	Yes
								Yes
								Yes
								Yes
								Yes
		Total-Impurities					(b) (4)	Yes
		Particulate Matter(≥10μm)	NN*	NN*	No trend	NN*	NN*	Yes
		Particulate Matter(≥25μm)	NN*	NN*	No trend	NN*	NN*	Yes

* NN=not necessary. The attribute is not significantly change over time
** NN=not necessary. If the model can't pool the slop, it has to have a separate intercept
***for model with separated regression lines for different lots, we take the lowest and highest confidence limits among the confidence limits of available lots

2. Introduction and Background

On Jan. 8, 2020, Office of Pharmaceutical Quality (OPQ) requested the CMC statistical team in Office of Biostatistics (OB) to evaluate the stability trends for NDA204485 (S-013). The OPQ CMC reviewer requested the OB reviewer to conduct analysis to determine if the applicant proposed 24-month refrigerated (2-8°C) shelf life with 12 months of time out of refrigeration at controlled room temperature (25°C) are supported by the applicant's provided stability study data. The stability-indicating attributes that amenable for statistical analysis, their stability specifications and units are summarized in **Table 2**.

Table 2: Summary of Stability-indicating Attributes that Amenable for Statistical Analysis

Attribute	LowerSpec**	UpperSpec**	Unit
pH		(b) (4)	NA*
Assay			% of label claim
			%
			%
			%
			%
			%
Total-Impurities			%
Particulate-Matter ≥10μm			/vial
Particulate-Matter ≥25μm			/vial

*NA=not applicable, no lower limit for the specification is required for this attribute;
**LowerSpec = lower bound for the stability specification for this attribute;
**UpperSpec = upper bound for the stability specification for this attribute.

The storage condition, length, storage length, orientation and lot number of the stability data provided by the Applicant that amenable for statistical analysis are summarized in **Table 3**. Among the three studies submitted by the Applicant, the Out of Refrigeration (OOR) study gives the worst condition for the shelf life proposed by the Applicant. Our analysis will be focusing on analyzing whether the 12 months OOR study data and its corresponded 95% confidence limits are within the specifications for the Applicant's proposed shelf life. More specifically, the proposed shelf life is acceptable if the 12 months OOR study data (and its 95% confidence limit) of the sample store at 25°C for 12 months after stored at 5°C for 12 months are within the stability specifications provided in **Table 2** for all ten attributes, both strengths and both orientations.

The applicant initially provided 6 months of sample stored at 25°C after stored at 5°C for 12 months for the OOR study in their original submission dated Dec. 20, 2019. After reviewing the original submitted data, we sent an information request to the applicant on Feb. 14, 2020. The IR asked the applicant to provide additional OOR study data for 3 months (if available), 9 months and 12 months. Since according to the applicant's data tables, the 9-month and 12-month data should be available in October 2019 and January 2020. The applicant responded to the IR on Feb. 21, 2020 and provided the requested data.

Table 3: Summary of the Applicant's Stability Data that Amenable for Statistical Analysis

Study	Storage condition and length of the Applicant's provided data	Strength	Orientation	Lot number
Refrigerated Study	18 months data of sample stored at 5 C	0.4U/mL	Inverted, upright	313657/313660 313658/313661 313659/313662
		0.6U/mL	Inverted, upright	313650/313654 313651/313655 313652/313656
Room Temperature Study	12 months data of sample store at 25 C	0.4U/mL	Inverted, upright	313657/313660 313658/313661 313659/313662
		0.6U/mL	Inverted, upright	313650/313654 313651/313655 313652/313656
Out of Refrigeration (OOR) Study	12 months data of sample stored at 25 C after stored at 5 C for 12 months	0.4U/mL	Inverted, upright	313657/313660 313658/313661 313659/313662
		0.6U/mL	Inverted, upright	313650/313654 313651/313655 313652/313656

The final statistical analysis is performed on the 12 months OOR study data for Lots 313650/313654, 313651/313655, 313652/313656, 313657/313660, 313658/313661 and 313659/313662 stored at 25°C for 0 month, 6 months, 9 months and 12 months after stored at 5°C for 12 months.

This review is focusing evaluate whether the 95% confidence limits of the data at the end of the OOR study are out of the stability specification for each attribute.

3. FDA Statistical Reviewers' Analyses

I conducted independent statistical analysis on OOR study data with two strengths 0.4U/mL and 0.6U/mL, two orientations Inverted and Upright for lots 313650/313654, 313651/313655, 313652/313656, 313657/313660, 313658/313661 and 313659/313662 for the sample stored t 25°C for 0 month, 6 months, 9 months and 12 months after stored at 5°C for 12 months. The analysis is conducted on 10 stability-indicating attributes (summarized in **Table 2**) that amenable for statistical analysis.

3.1 Statistical Analysis for Stability-Indicating Attributes

Since the requirement for statistical analysis for OOR data was not provided by any FDA guidance, the current analysis is following the statistical modeling approaches provided by the ICH Q1E guidance.

3.1.1 Model Determination for Lots Using ANCOVA

According to the ICH Q1E guidance, analysis of covariance (ANCOVA) can be employed, where time is considered the covariate, to test the significance of trend verses time, as well as the differences in slopes and intercepts of the regression lines among lots. Four cases can be considered for different p-values for time, slopes an intercepts.

- If the time trend isn't significant, no statistical model is necessary
- If P-slop<0.25, use regression model with separated slop, separated intercept
- If P-slop≥0.25, P-intercept<0.25, use regression model with pooled slop, separated intercept
- If P-slop≥0.25, P-intercept≥0.25, use regression model with pooled slop, pooled intercept

3.1.2 Shelf Life Estimation Using Regression Models

The summary of the regression analysis results can be found in **Table 1**, it shows the regression model and whether the applicant's proposed shelf-life is supported by the OOR study data for each stability-indicating attribute with different orientations and strengths. Moreover, the stability plots of regression analysis results can also be found in Error! Reference source not found. **to 4** (Appendix), respectively. For different lots, the observed data are shown in circle (o), triangle (Δ) and cross (×) shapes with different colors; the predicted mean values obtained by linear regression (regression lines) are shown in solid lines; the corresponding 95% confidence limit(s) of the mean values are shown in dashed lines; the acceptance criteria are shown in solid line with green color. For each regression line, the proposed shelf life is acceptable if the 95% confidence limit(s) of the mean value have not intercepted with the acceptance criteria at the end of the proposed shelf life.

3.2 Summary of Regression Analysis Results

The regression analysis results for each stability-indicating attribute that amenable for statistical analysis are summarized as follows:

- **pH**: No significant trend over time and all values are within specification. Stability data and analysis results are illustrated in **Table 1**.
- **Assay**: Significant change and decreasing trend can be seen in the OOR study data. For both strengths, the OOR study data with inverted orientation can be fitted by regression model with separated slops and separated intercepts, while the OOR study data with upright orientation need to be fitted by regression model with pooled slop but separated intercepts. The regression line(s) as well as its two-sided 95% confidence limit(s) are within the specification at the end of OOR study. Stability data and analysis results are illustrated in **Table 1** and **Figure 1.1, 2.1, 3.1, 4.1**.
- (b) (4) Significant change and increasing trend can be seen in the OOR study data. For 0.4U/mL strength with both orientations and 0.6U/mL strength with inverted orientation, the OOR study data can be fitted by regression model with pooled slop and pooled intercept. While, for 0.6U/mL strength with upright orientation, the OOR study data need to be fitted by regression model with separated slops and separated intercepts. The regression line(s) as well as its one-sided 95% confidence limit(s) are within the specification at the end of OOR study. Stability data and analysis results are illustrated in **Table 1** and **Figure 1.2, 2.2, 3.2, 4.2**.
- (b) (4) Significant change and increasing trend can be seen in the OOR study data. For both strengths with both orientations, the OOR study data can be fitted by regression model with pooled slop and pooled intercept. The regression line(s) as well as its one-sided 95% confidence limit(s) are within the specification at the end of OOR study. Stability data and analysis results are illustrated in **Table 1** and **Figure 1.3, 2.3, 3.3, 4.3**.
- (b) (4) No significant trend over time and all values are within specification. Actually, the observed values are (b) (4)% all the time. Stability data and analysis results are illustrated in **Table 1**.
- (b) (4) Significant change and increasing trend can be seen in the OOR study data. For both strengths with both orientations, the OOR study data can be fitted by regression model with pooled slop and pooled intercept. The regression line(s) as well as its one-sided 95% confidence limit(s) are within the specification at the end of OOR study. Stability data and analysis results are illustrated in **Table 1** and **Figure 1.4, 2.4, 3.4, 4.4**.

- [redacted] No significant trend over time and all values are within specification. Actually, the observed values are [redacted]% all the time. Stability data and analysis results are illustrated in **Table 1**.
- **Total Impurities**: Significant change and increasing trend can be seen in the OOR study data. For both strengths with both orientations, the OOR study data can be fitted by regression model with pooled slop and pooled intercept. The regression line(s) as well as its one-sided 95% confidence limit(s) are within the specification at the end of OOR study. Stability data and analysis results are illustrated in **Table 1** and **Figure 1.5, 2.5, 3.5, 4.5**.
- **Particulate Matter(≥10 μm)**: No significant trend over time and all values are within specification. Stability data and analysis results are illustrated in **Table 1**.
- **Particulate Matter(≥25 μm)**: No significant trend over time and all values are within specification. Stability data and analysis results are illustrated in **Table 1**.

4. Conclusions and Recommendations

Based on my independent analysis on the provided OOR study data (12 months data of the sample stored at 25°C after stored at 5°C for 12 months) for ten stability-indicating attributes that amenable for statistical analysis are pH, Assay, [redacted] Total Impurities, Particulate Matter(≥10 μm), Particulate Matter(≥25 μm) with two strengths 0.4U/mL and 0.6U/mL, two orientations Inverted and Upright, our conclusions are summarized in **Table 1** and below:

- a 24-month refrigerated (2-8°C) shelf life with 12 months of time out of refrigeration at controlled room temperature (25°C) are supported by the statistical analysis on the OOR Study data

Appendix

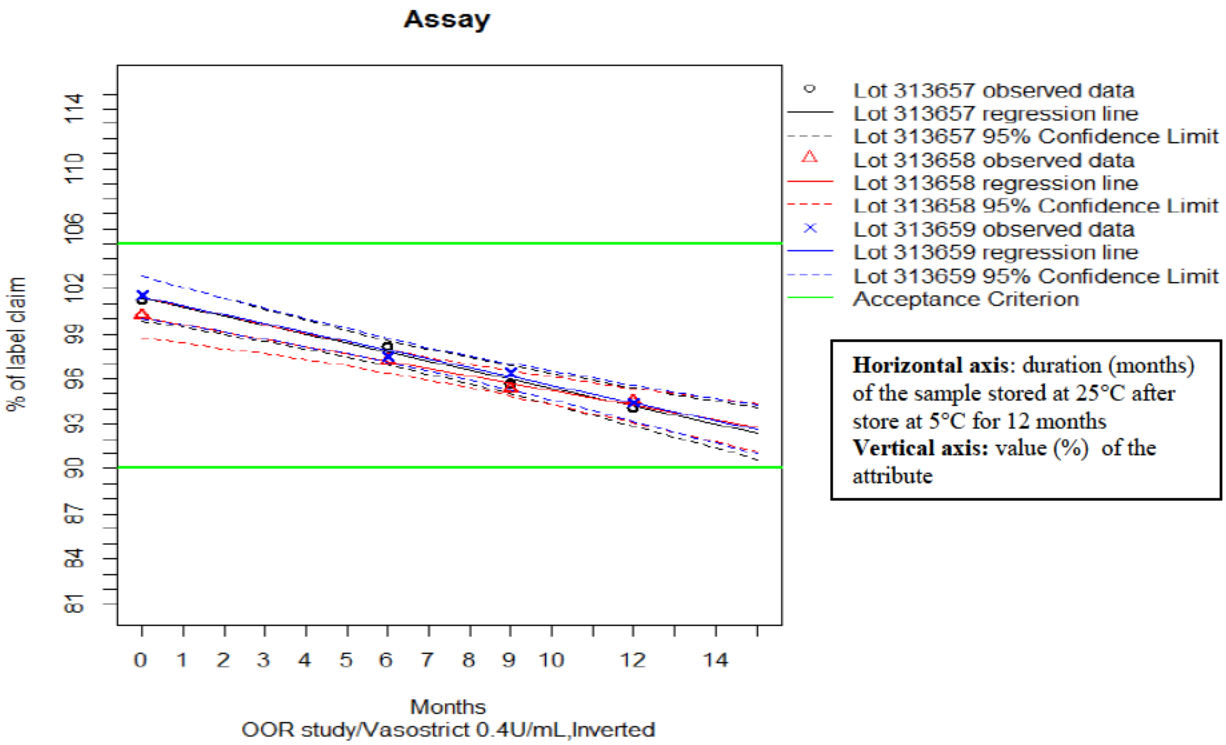


Figure 1.1. Regression lines for Assay, OOR study: Vasostrict 0.4U/mL, Inverted

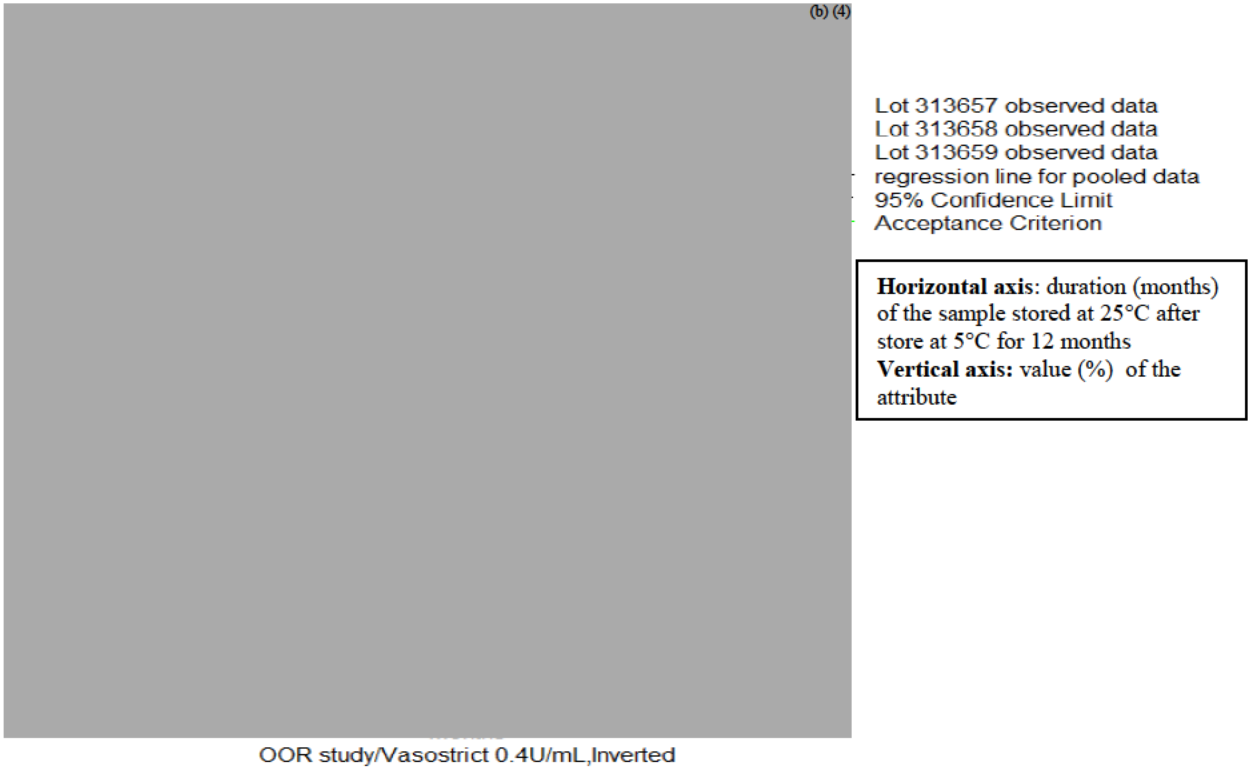


Figure 1.2. Regression lines for (b) (4), OOR study: Vasostrict 0.4U/mL, Inverted

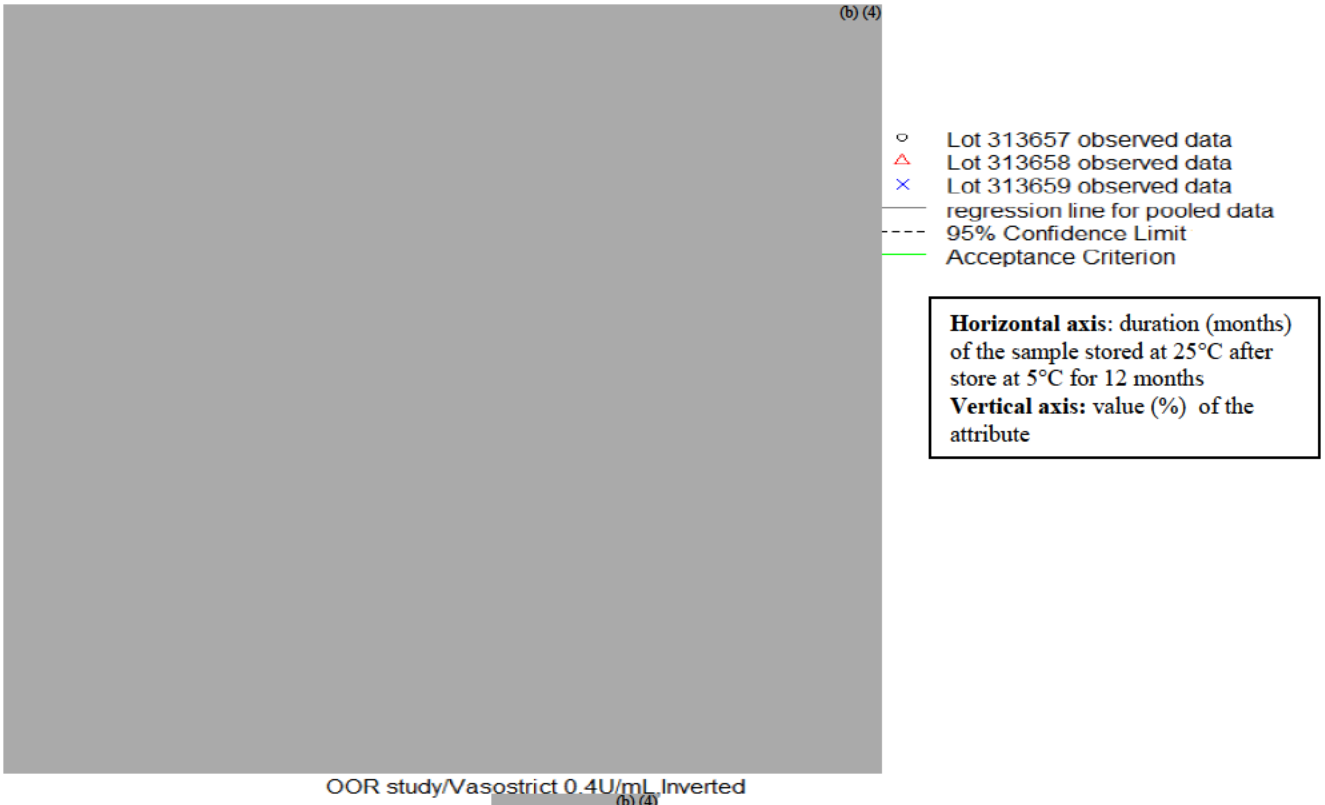


Figure 1.3. Regression lines for (b) (4) OOR study: Vasostrict 0.4U/mL, Inverted

Figure 1.4. Regression lines for (b) (4) OOR study: Vasostrict 0.4U/mL, Inverted

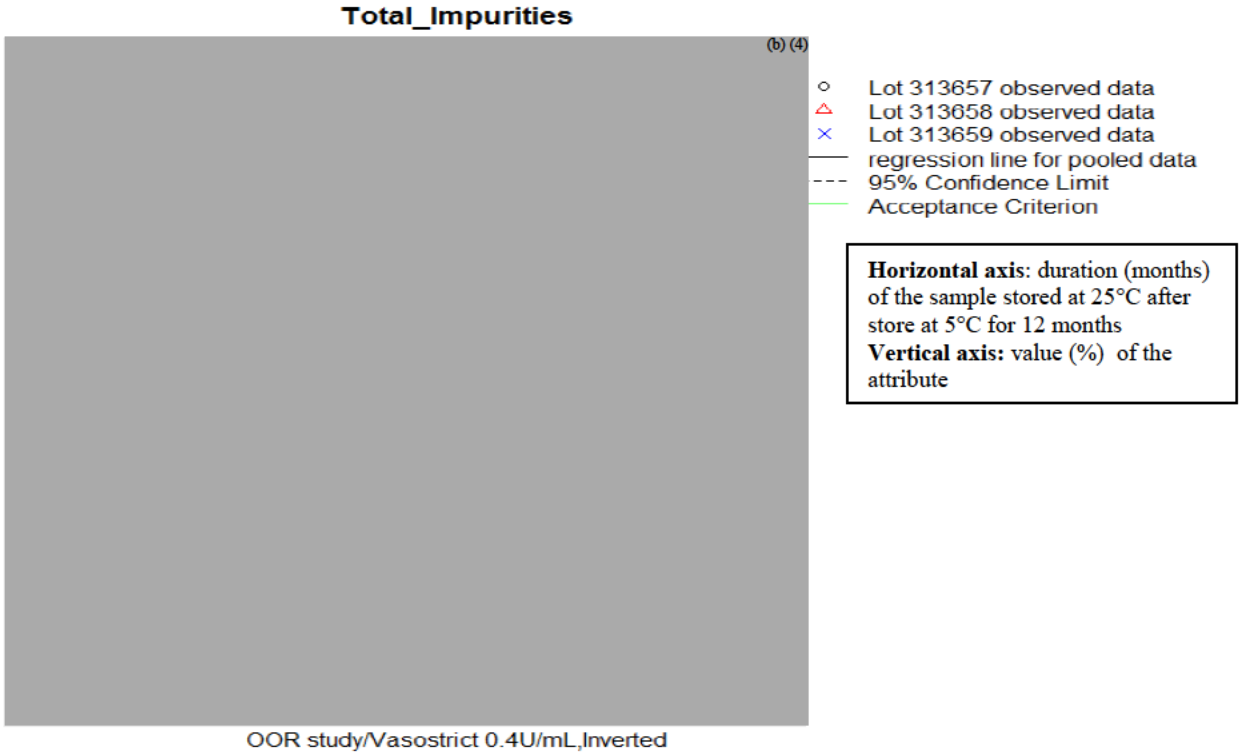


Figure 1.5. Regression lines for Total Impurities, OOR study: Vasostrict 0.4U/mL, Inverted

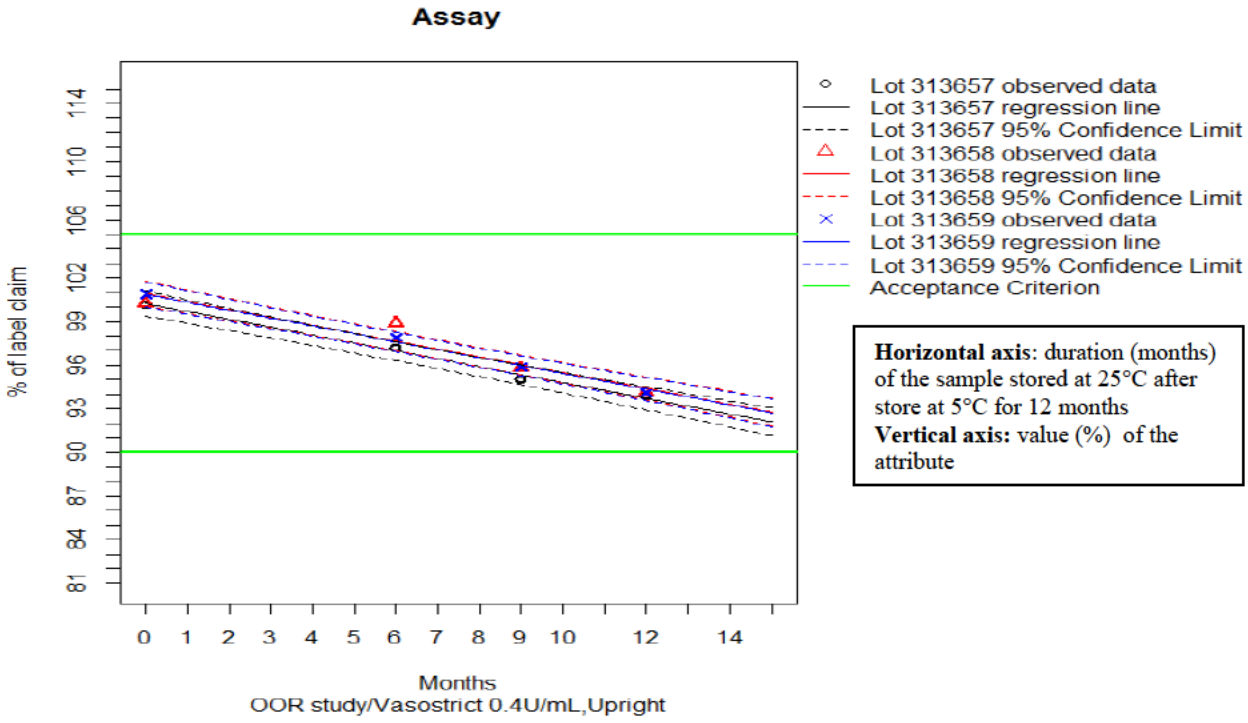


Figure 2.1. Regression lines for Assay, OOR study: Vasostrict 0.4U/mL, Upright

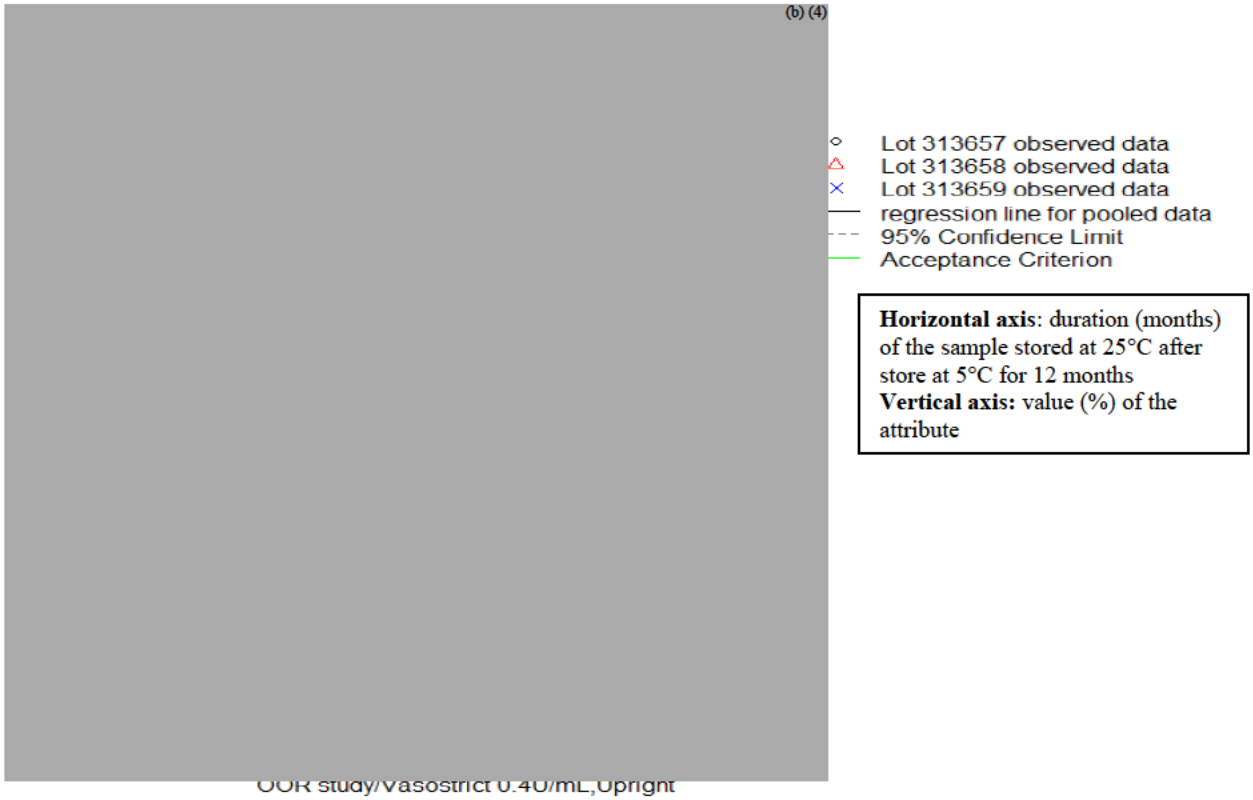


Figure 2.2. Regression lines for (b) (4) OOR study: Vasostrict 0.4U/mL, Upright

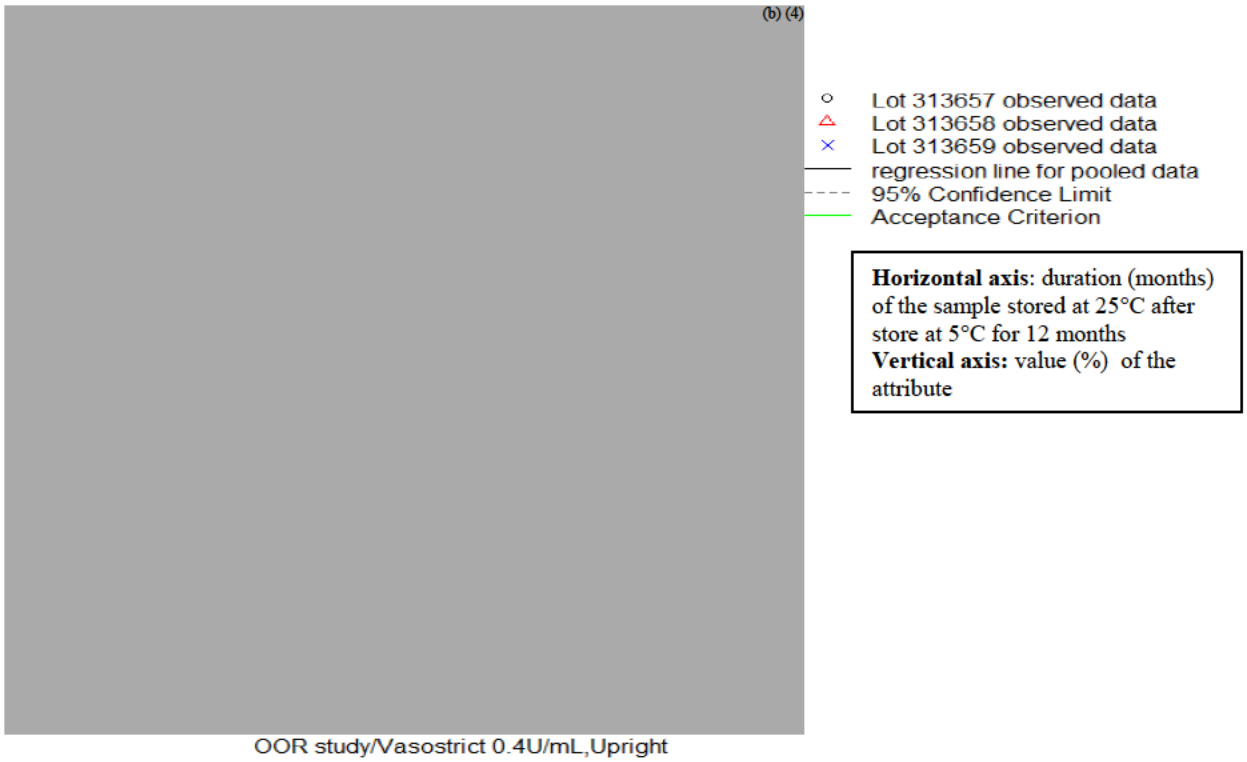


Figure 2.3. Regression lines for (b) (4), OOR study: Vasostrict 0.4U/mL, Upright

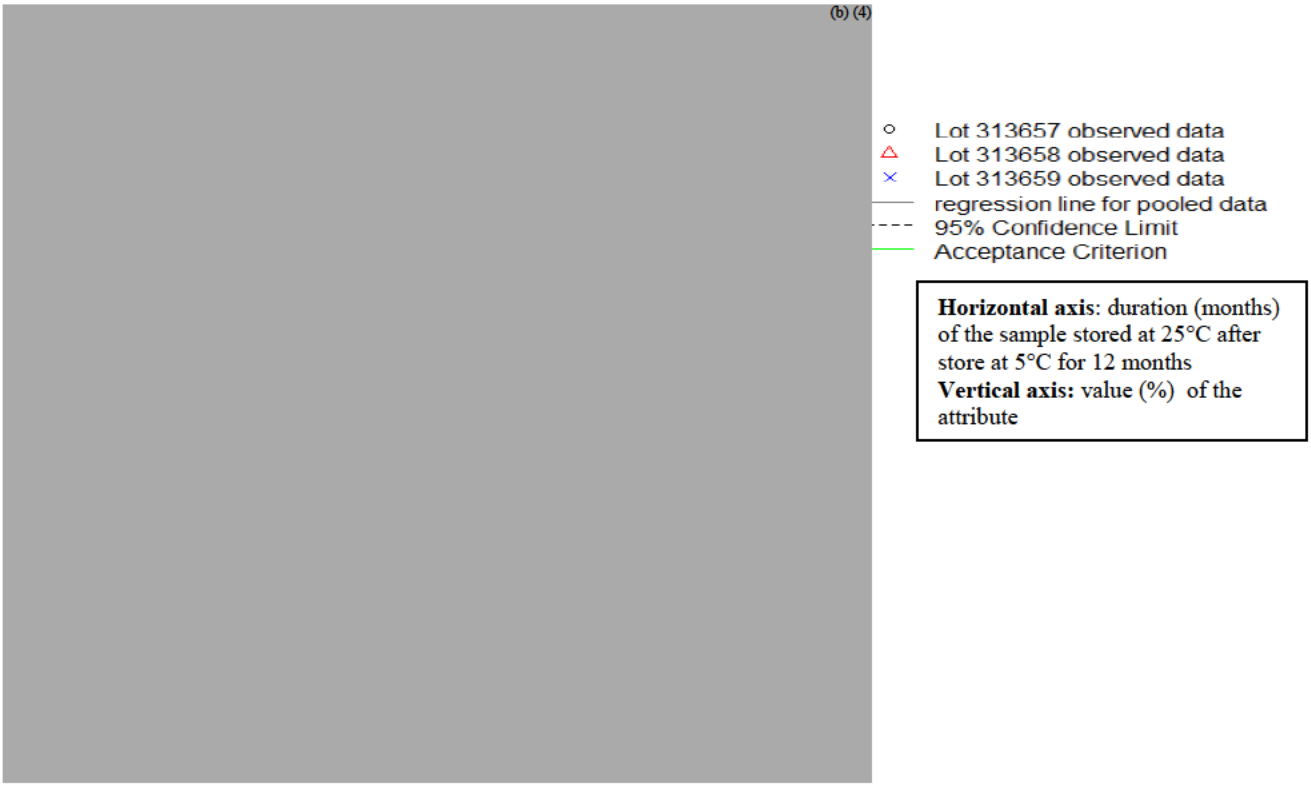


Figure 2.4. Regression lines for (b) (4) OOR study: Vasostrict 0.4U/mL, Upright

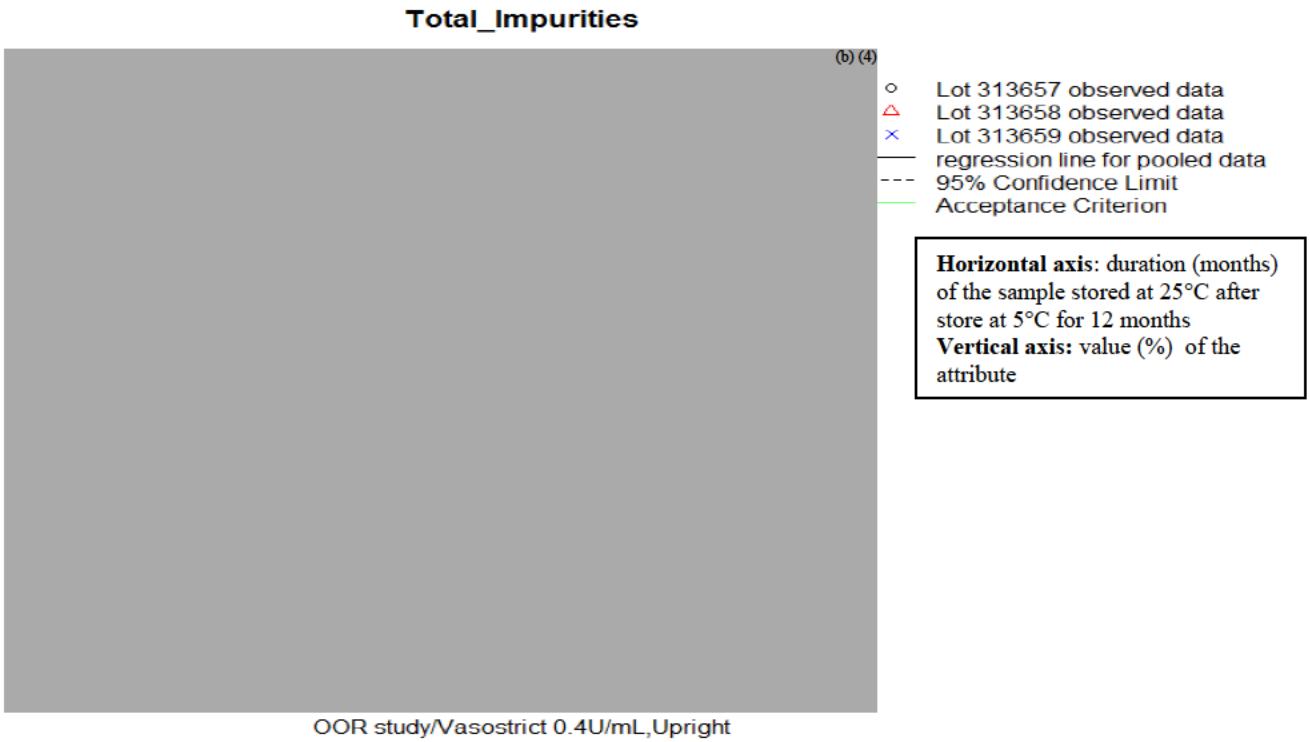


Figure 2.5. Regression lines for Total_Impurities, OOR study: Vasostrict 0.4U/mL, Upright

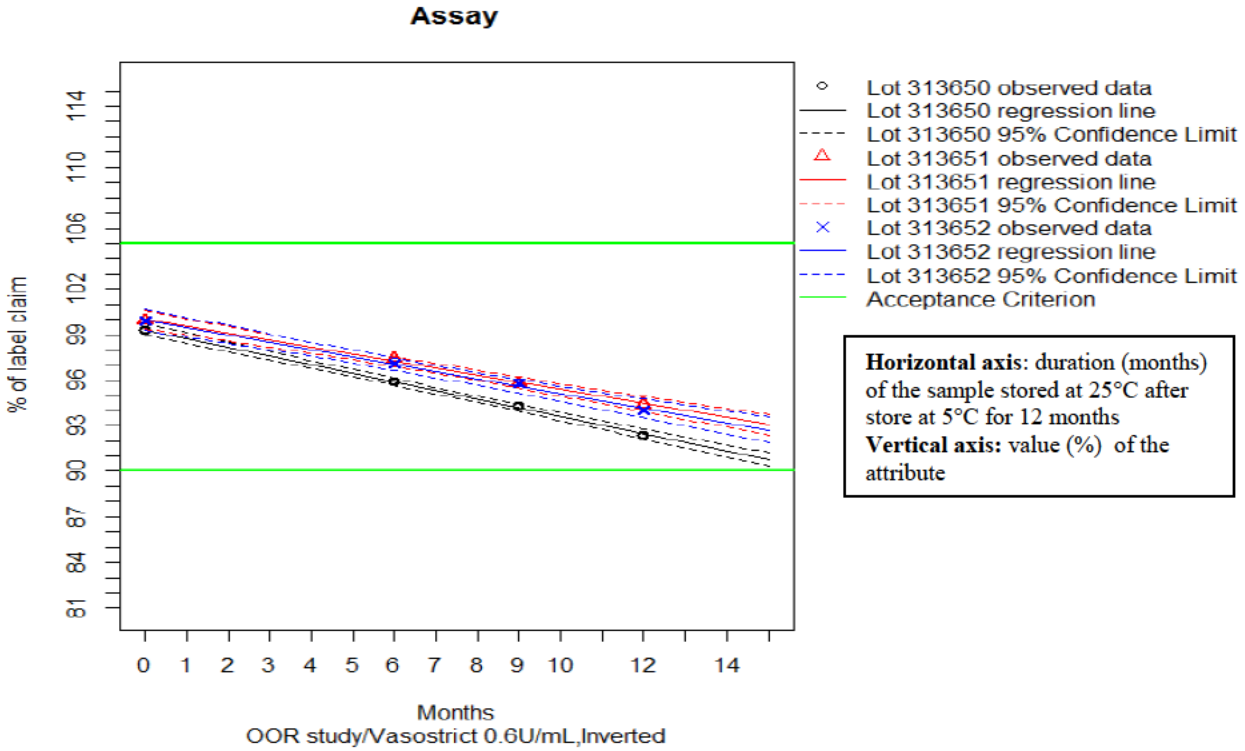


Figure 3.1. Regression lines for Assay, OOR study: Vasostrict 0.6U/mL, Inverted

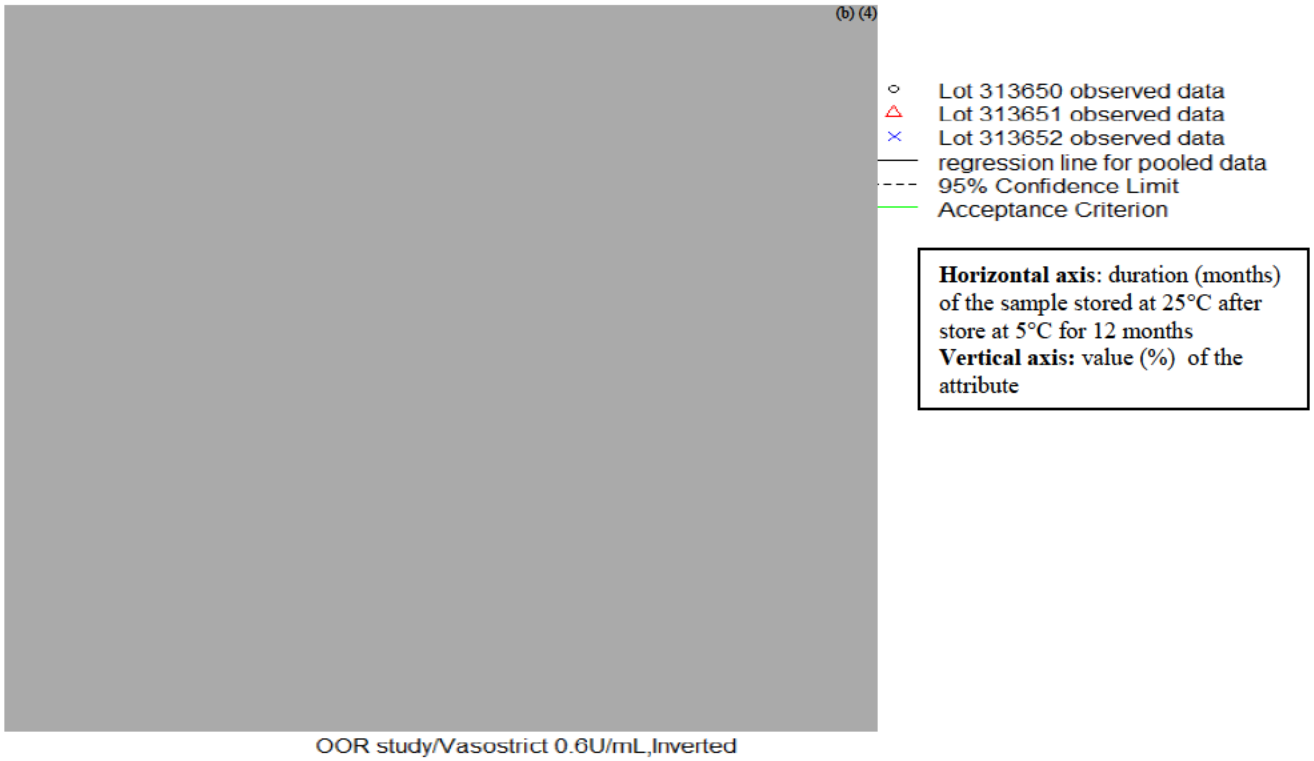


Figure 3.2. Regression lines for (b) (4), OOR study: Vasostrict 0.6U/mL, Inverted

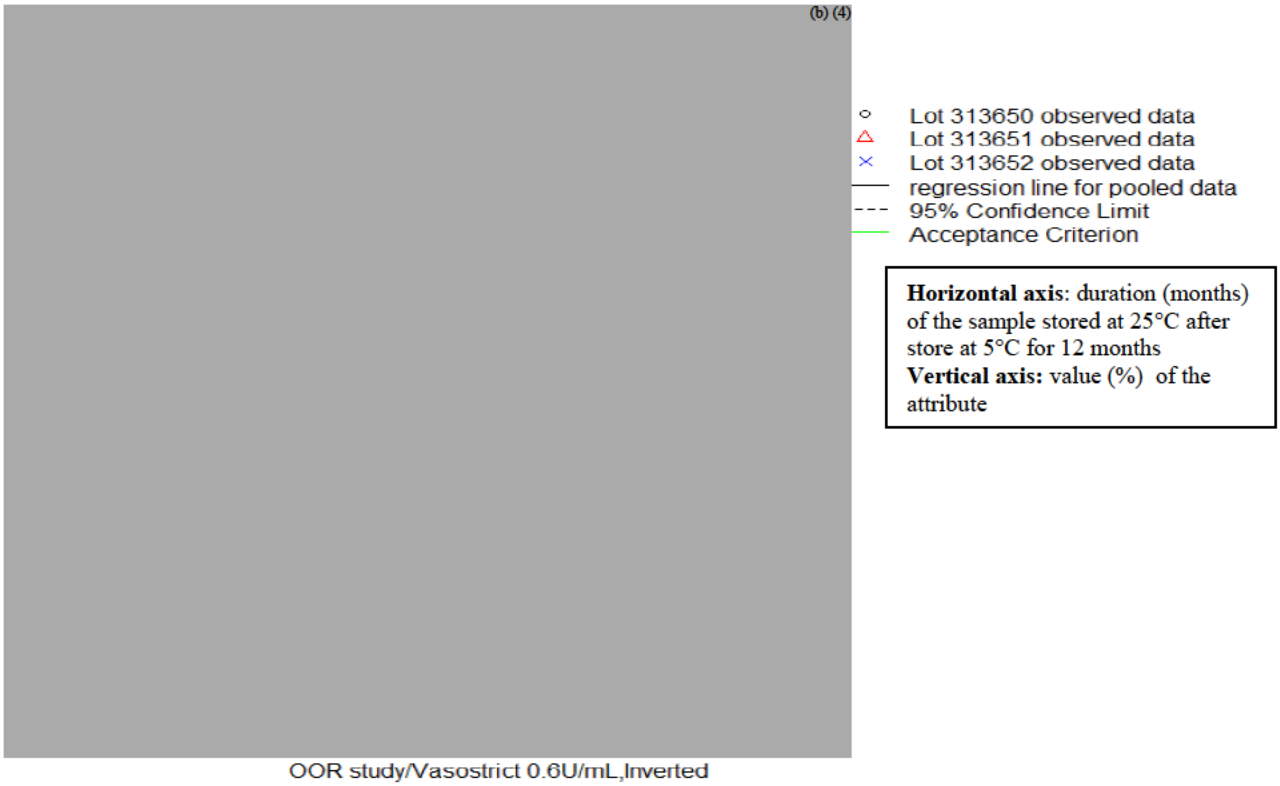


Figure 3.3. Regression lines for (b) (4) P, OOR study: Vasostrict 0.6U/mL, Inverted

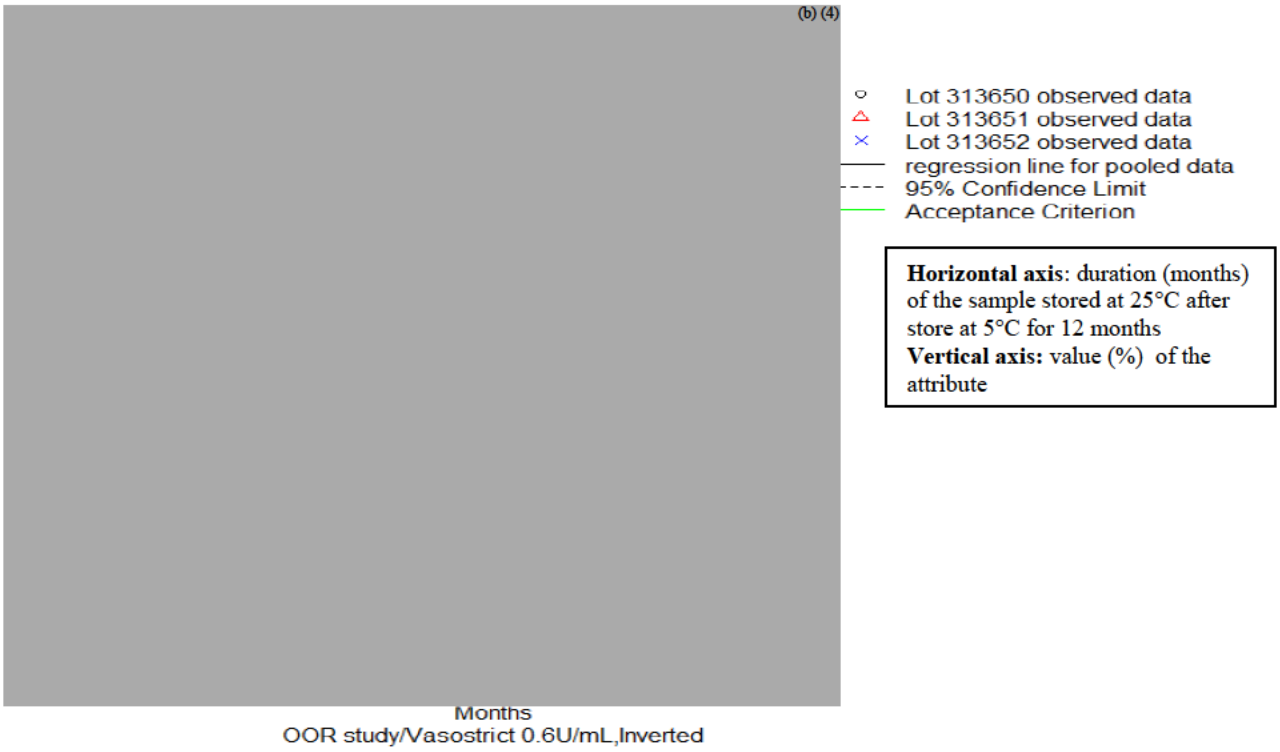


Figure 3.4. Regression lines for (b) (4) OOR study: Vasostrict 0.6U/mL, Inverted

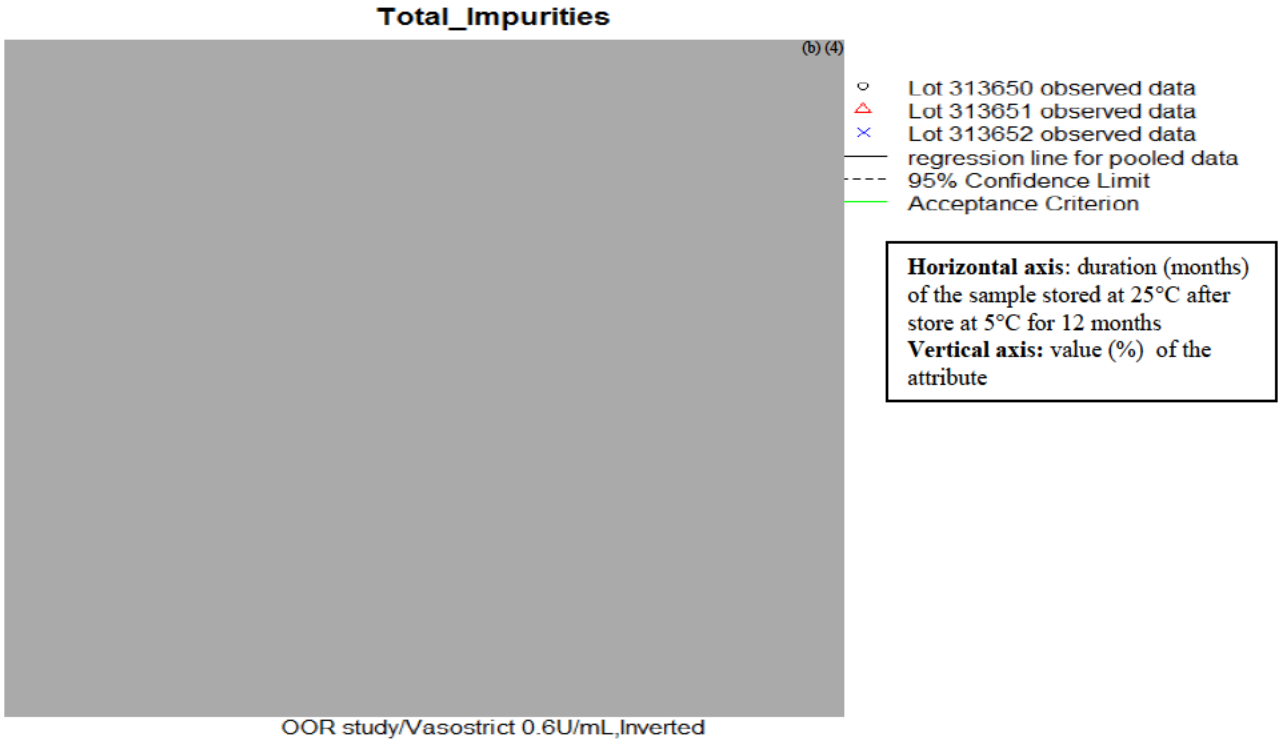


Figure 3.5. Regression lines for Total Impurities, OOR study: Vasostrict 0.6U/mL, Inverted

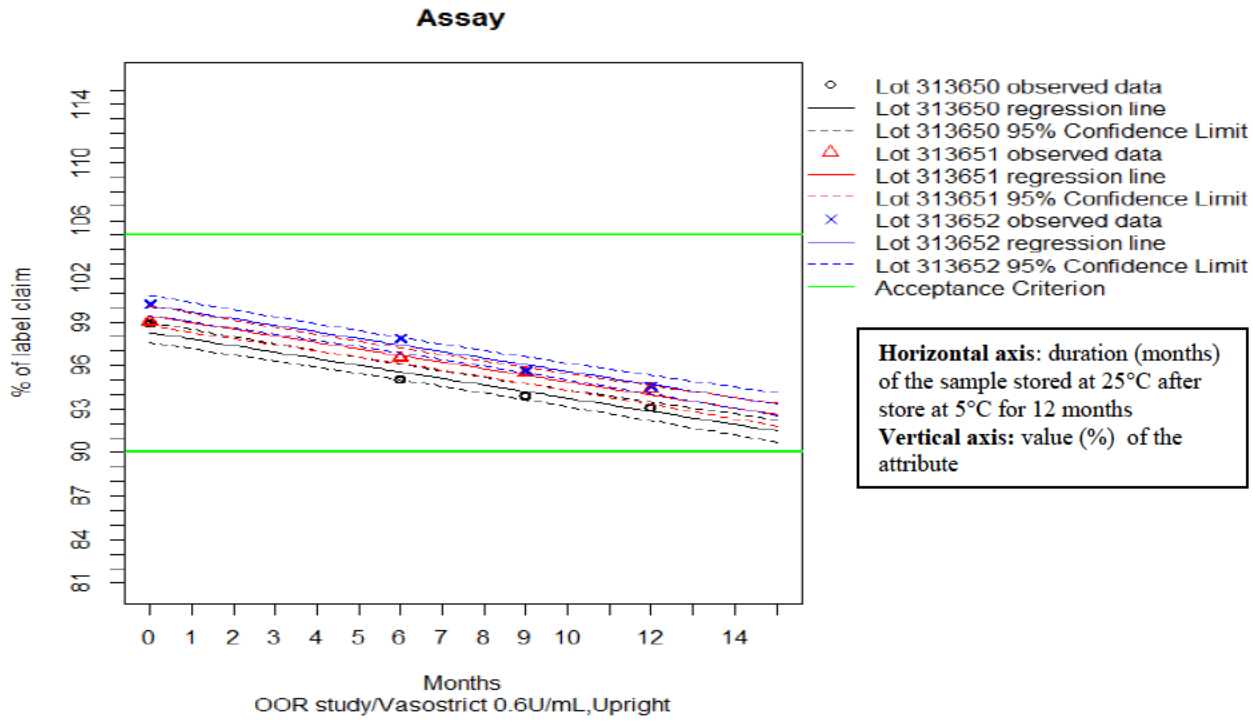


Figure 4.1. Regression lines for Assay, OOR study: Vasostrict 0.6U/mL, Upright

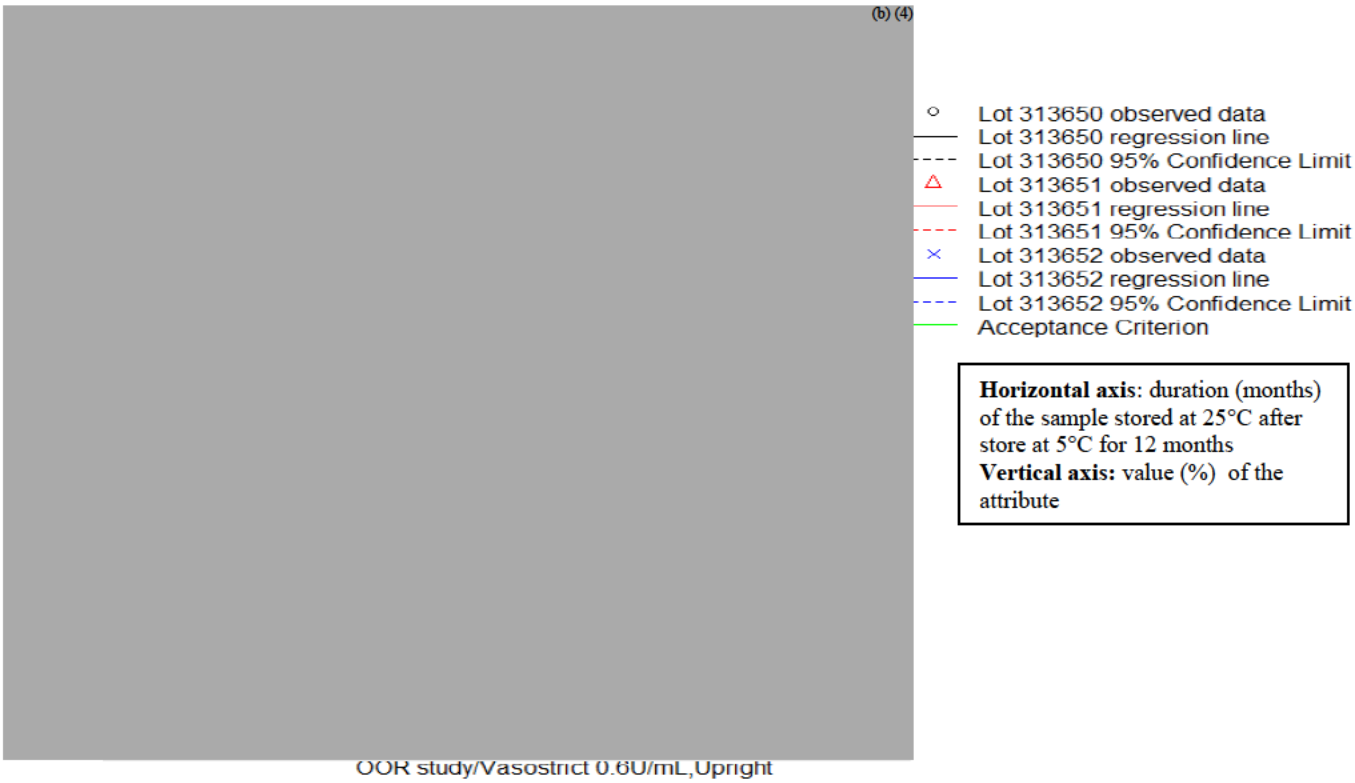


Figure 4.2. Regression lines for (b) (4), OOR study: Vasostrict 0.6U/mL, Upright

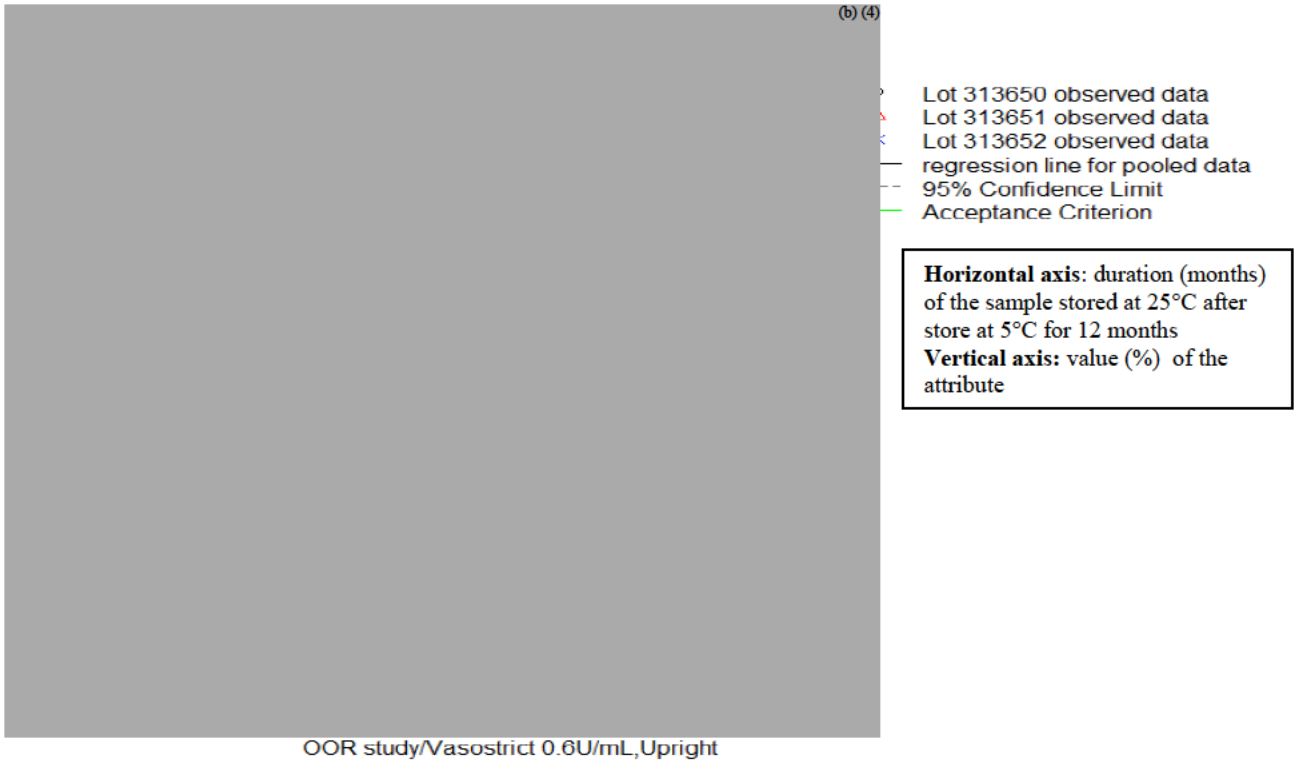


Figure 4.3. Regression lines for (b) (4) OOR study: Vasostrict 0.6U/mL, Upright

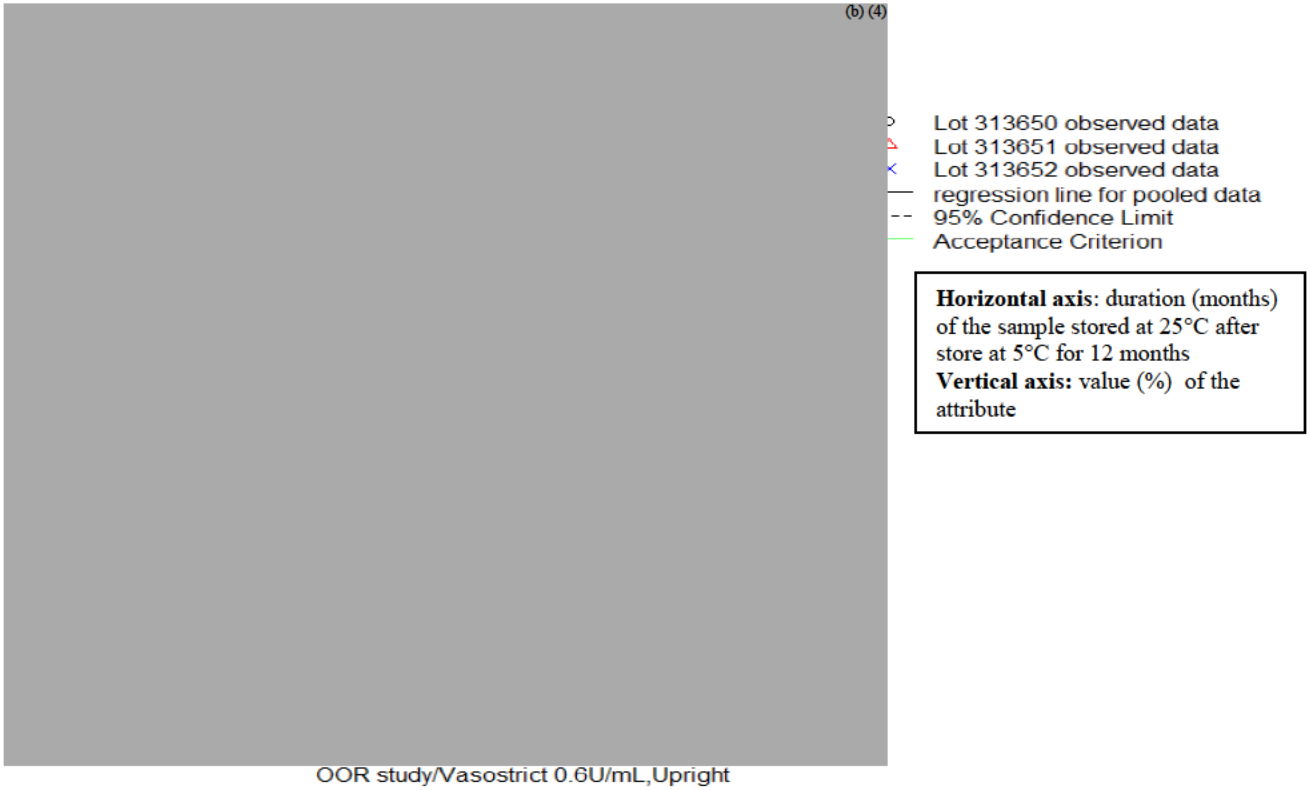


Figure 4.4. Regression lines for (b) (4) OOR study: Vasostrict 0.6U/mL, Upright

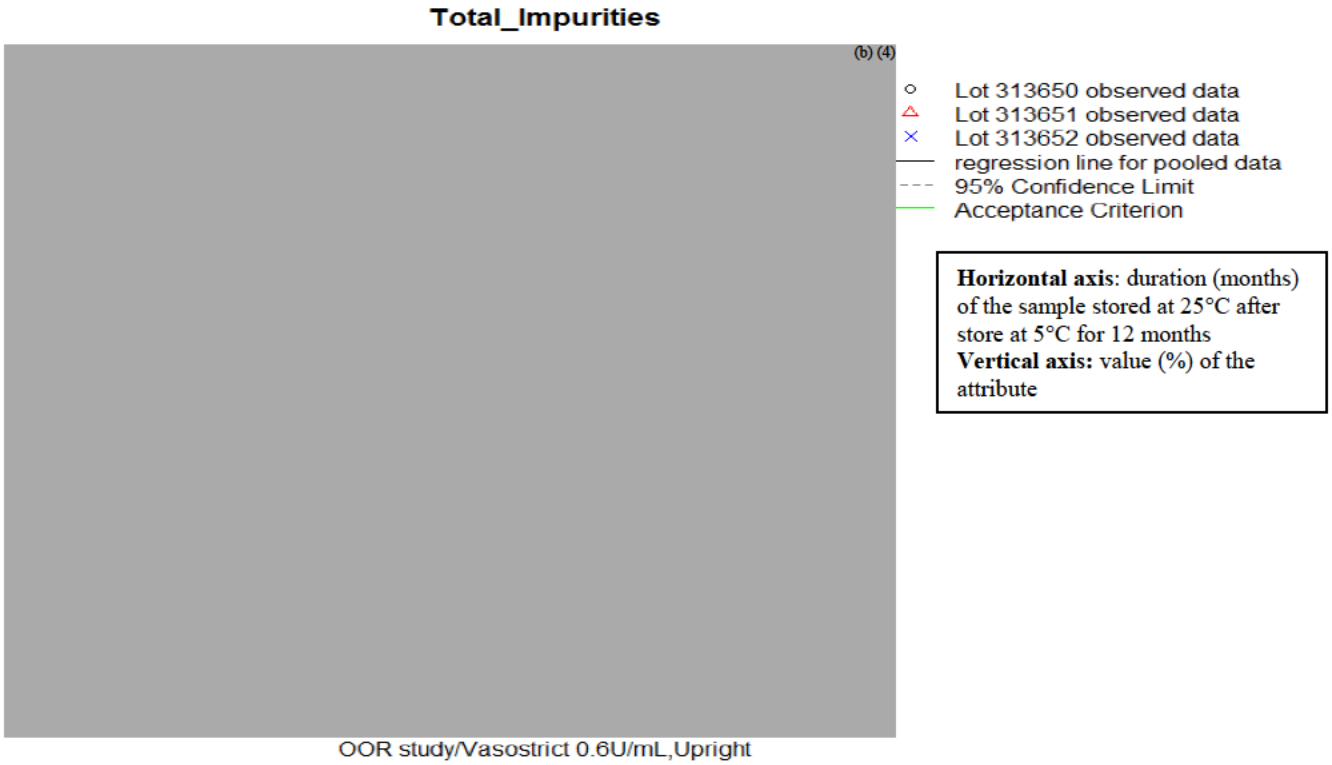


Figure 4.5. Regression lines for Total_Impurities, OOR study: Vasostrict 0.6U/mL, Upright

---

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/

XIAOYU CAI
03/09/2020 01:15:23 PM

MEIYU SHEN
03/09/2020 01:55:11 PM

YI TSONG
03/09/2020 01:57:33 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204485Orig1s013

MICROBIOLOGY/VIROLOGY REVIEW(S)

CHAPTER VII: MICROBIOLOGY

IQA NDA Assessment Guide Reference

Product Information	
NDA Number	204485/S013
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Vasopressin injection, USP, 20 units/mL (Single-dose), 200 units/10mL (Multi-dose), adding 40 units/100 mL and 60 units/100 mL (Single-dose) premixed solutions within this submission.
Route of Administration	Continuous Intravenous infusion
Applicant Name	Par Sterile Products, LLC
Therapeutic Classification/ OND Division	Division of Cardiovascular and Renal Products
Manufacturing Site	Par Sterile Products, LLC 870 Parkdale Road, Rochester, MI 48307, USA
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

The drug product is (b) (4) (b) (4)

List Submissions being assessed (table):

Document(s) Assessed	Date Received
eCTD Seq #0083 (PAS original)	December 20, 2019
eCTD Seq #0105 (Stability data)	February 21, 2020
eCTD Seq #0106 (Labelling)	March 6, 2020
eCTD Seq #0109 (IR response)	April 6, 2020

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The December 20, 2019 PAS requests the addition of 40 units/100 mL and 60 units/100 mL single dose premixed vial presentations. The applicant will use a new 100 mL container for these presentations.

Concise Description of Outstanding Issues
(List bullet points with key information and update as needed):
None

Supporting Documents:
DMF [redacted] (type V) [redacted] M16R01.doc, dated January 2, 2020. [redacted] (adequate)

The December 20, 2019 PAS requests the addition of two new drug product presentations. These will be ready to inject and do not require dilution prior to injection. These include a 40 units/100 mL and 60 units/100 mL single dose vial configurations in new 100 mL vials. The applicant proposes bulk batch sizes of [redacted] and [redacted] for these new presentations and provided [redacted] validation data to support the new formulations. Validation data to support [redacted] of the new container size and representative stopper [redacted] data was provided.

P.1 Description of the Composition of the Drug Product

- **Description of drug product:** A sterile solution for intravenous administration currently approved as 20 units/1 mL in a single dose vial and 200 units/10 mL in a multi-dose vial. Both of these configurations require additional dilution, and this PAS proposes new single dose, ready to use, diluted configurations of 40 units/100mL and 60 units/100 mL in 100 mL vials.

- **Approved Drug product composition:**

Ingredient	20 units / mL Single dose configuration Content per mL	20 units /mL Multi-dose configuration Content per mL
Vasopressin, USP	20 units	20 units
Chlorobutanol, NF	N/A	5 mg
Sodium acetate [redacted]	[redacted]	[redacted]
Water for injection, USP	[redacted]	[redacted]

- **Proposed Drug product composition:**

Ingredient	40 units /100 mL configuration Content per mL	60 units /100mL configuration Content per mL
Vasopressin, USP	0.4 units	0.6 units
Dextrose Anhydrous, [redacted]	[redacted]	[redacted]
Sodium acetate [redacted]	[redacted]	[redacted]
Sodium hydroxide, [redacted]	[redacted] pH 3.8	[redacted] pH 3.8
Hydrochloric acid, [redacted]	pH 3.8	pH 3.8
Water for injection, USP	[redacted]	[redacted]

- **Description of proposed container closure system:**

Component		
Vial	(b) (4)	
Stopper		
Cap 40 units/100 mL configuration		
Cap (60 units/100 mL configuration		

Reviewer's Assessmen
The applicant provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

(b) (4)

(b) (4)

The applicant also provided validation data to support the use of the (b) (4) for container closure integrity testing as part of the stability program.

Antimicrobial Effectiveness Testing
(3.2.P.1 Description and Composition)

This supplement proposes to add two new configurations which are both to be used as single dose, without dilution. Thus antimicrobial effectiveness testing is not required.

Adequate

Reviewer's Assessment:
The applicant is proposing two new single dose configurations and thus antimicrobial effectiveness testing is not required.

P.3 Manufacture

P.3.1 Manufacturers

The applicant has not proposed any changes to the facility which will manufacture the drug product.

Adequate

Reviewer's Assessment:
The applicant will continue to manufacture the drug product at the manufacturing location located in Rochester, MI.

(b) (4)

[redacted]

13 Page(s) have been Withheld in Full as b4 (TS/CS) immediately following this page

Calculated endotoxin dose at the proposed endotoxins specification and maximum dose for the 40 units/100 mL configuration:

(b) (4)

Adequate

Reviewer's Assessment:
The applicant provided an acceptable routine testing dilution and the endotoxin dose at the proposed endotoxins specification and maximum dose as calculated by this

(b) (4)

(b) (4)

Adequate

Reviewer's Assessment:
The applicant provided an acceptable summary of the sterility test validation.

P.7 Container Closure

Summary table of the container closure system proposed

Not Applicable

Reviewer's Assessment: See section P.1

P.8 Stability

P. 8.1 Stability Summary and Conclusion

(3.2.P.8.1 Stability Summary)
The applicant proposes an expiry of 24 months refrigerated (2-8 °C) and up to 12 months at room temperature to be consistent with current labelling.

Adequate

Reviewer's Assessment:
The applicant's proposed 24 month expiry is acceptable and consistent with the previously approved configurations.

The applicant provided an acceptable stability program for microbial testing. The (b) (4) container closure integrity method was evaluated in section P2 Pharmaceutical Development of this review. Please see the container/closure and package integrity section above for additional details.

P.8.3 Stability Data

(3.2.P.8.3 Stability data)
The applicant provided bacterial endotoxin and sterility data up to 18 months.

Adequate

Reviewer's Assessment:
The applicant provided acceptable microbiology stability data.

A Appendices

A.2 Adventitious Agents Safety Evaluation

Not Applicable

Reviewer's Assessment:

A.2.1 Materials of Biological Origin

Not Applicable

Reviewer's Assessment:

A.2.2 Testing at Appropriate Stages of Production

Not Applicable

Reviewer's Assessment:

A.2.3. Viral Testing of Unprocessed Bulk

Not Applicable

Reviewer's Assessment:

A. 2.4 Viral Clearance Studies

Not Applicable

Reviewer's Assessment:

R Regional Information

Executed Batch Records

The batch records confirm that validated (b) (4) manufacturing processes were used for the manufacture of the exhibit batches.

Adequate

Reviewer's Assessment:

The applicant provided detailed batch records, which used the described manufacturing processes.

Comparability Protocols

(3.2.P 3.2.R.2.P)

None Provided

Adequate

Reviewer's Assessment:
The applicant did not provide any comparability protocols.

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

(1.14.1.2 Insert – Tracked changes, page 8)
Storage: 2-8 °C, vials maybe held for up to 12 months at room temperature (20 to 25 °C)
Route of administration: Intravenous administration
Container: 100 mL Single dose vials

The package insert states to mark vials to indicate the revised 12 month expiration date after removal from refrigeration. If the original manufacturer's expiration date is shorter than the revised expiration, then the shorter date must be used.

Adequate

Reviewer's Assessment:
The applicant provided acceptable instructions for handling the single dose 100 mL vials.

MICROBIOLOGY LIST OF DEFICIENCIES

None

Primary Microbiology Assessor Name and Date:
David Bateman, Ph.D. (April 7, 2020)

Secondary Assessor Name and Date (and Secondary Summary, as needed
Erika Pfeiler, Ph.D. (April 10, 2020)

Erika Pfeiler

Digitally signed by Erika Pfeiler
Date: 4/10/2020 01:02:24PM
GUID: 502d1da500002b6a73a00c0e0dff6e1d

David Bateman

Digitally signed by David Bateman
Date: 4/10/2020 01:04:22PM
GUID: 5463e4f2002198d458a8bff3d150a8ed

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204485Orig1s013

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

BIOPHARMACEUTICS ASSESSMENT Office of New Drug Products		
Application No.	NDA-204485-SUPPL-13	
Applicant	Par Sterile Products LLC	
OND Division	Division of Cardiovascular and Renal Products (DCRP)	
Trade Name	Vasostrict®	
Generic Name	Vasopressin injection, USP	
Dosage Form	Intravenous injection	
Strength(s)	Approved: 20 units/ mL, 200 units/10 mL, Proposed: 40 units/100 mL and 60 units/100 mL	
Route of Administration	Continuous IV infusion	
Indication	To increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.	
Submission Date(s)	12/20/2019	
Type of Submission	Prior Approval Supplement (PAS)	
Date of Assigned	01/09/2020	
Date of Review	03/15/2020	
Due Date	**Review**	**PDUFA**
	03/30/2020	04/20/2020
Primary Reviewer	Huong Moldthan, Ph.D.	
Secondary Reviewer	Poonam R. Delvadia, Ph.D.	
Key Review Points	**The Supplement proposes:** Addition of Vasostrict® 40 units/100 mL and 60 unit/100 mL premixed formulations. **Biopharmaceutics review focuses on the evaluation of:** Bridging Vasostrict® 40 units/100 mL and 60 unit/100 mL premixed formulation to current approved strengths of 20 units/mL (single use vial) and 200 units/10 mL (multiple use vial).	
Recommendation	***ADEQUATE***	

EXECUTIVE SUMMARY

Background:

The NDA-204485 for Vasostrict® (vasopressin injection, USP) was approved on 04/17/2014 under 505(b)(2) of the Federal Food, Drug and Cosmetic Act (FDCA) for the marketing of Vasopressin injection, USP with two strengths of 20 units/mL and 200 units/10mL.[1]

[1] \\cdsesub1\evsprod\nda204485\0083\m1\us\cover-letter.pdf

Submission:

This PAS submission is seeking approval of additional presentations of a 40 units/100 mL and a 60 units/100 mL single dose vial for the same indication, route of administration and dosage form as the current approved Vasostrict® presentations. The proposed presentations will not need further dilution prior to administration (premixed) when compared to approved presentation that needs to be diluted before administration. The Applicant provided side-by side comparison of qualitative compositions between the proposed product and current approved drug product (Table 1). [1]

Table 1. Details of the approved presentations and proposed new premixed presentations for Vasopressin IV administration

Conditions	Approved – Vasostrict Presentations		Proposed – Vasostrict Premixed Presentations	
Strength	20 units/mL	200 units/10 mL	40 units/100 mL	60 units/100 mL
Dosage Form	Injection	Injection	Injection	Injection
Route of Administration	Intravenous	Intravenous	Intravenous	Intravenous
Active (vasopressin)	20 units/mL	20 units/mL	0.4 units/mL	0.6 units/mL
Excipients	• Sodium Acetate (buffering agent) (b) (4) • Water for Injection	• Chlorobutanol (preservative) • Sodium Acetate (buffering agent) (b) (4) • Water for Injection	• Dextrose Anhydrous (b) (4) • Acetic Acid (b) (4) • Sodium Acetate (b) (4) • Sodium Hydroxide* • Hydrochloric Acid* • Water for Injection	• Dextrose Anhydrous (b) (4) • Acetic Acid (b) (4) • Sodium Acetate (b) (4) • Sodium Hydroxide* • Hydrochloric Acid* • Water for Injection
Container Configuration	1 mL glass vial	10 mL glass vial	100 mL glass vial	100 mL glass vial

*pH adjustment

Assessment:

The biopharmaceutics assessment focuses on the evaluation of the information submitted to bridge the proposed premixed and approved Vasostrict® presentations. The formulation of the proposed drug product is not qualitatively and quantitatively the same as the formulation of the approved drug product. Therefore, Information Request was sent on 02/13/2020 requesting additional information in support of bridging the proposed and approved products under 3420.24(b)(6) (Appendix). The complete response was received on 02/21/2020. Data provided demonstrates that the difference in inactive ingredients will not affect on distribution or elimination of drug substance in vivo. Comparative physiochemical results between approved and proposed Vasostrict® presentations are acceptable and will not impact the efficacy and safety of the proposed drug product.

Recommendation:

The information submitted in NDA-204485-SUPPL-13 adequately bridges the approved and proposed Vasostrict® presentations. ***This supplement is therefore recommended for Approval from a Biopharmaceutics perspective.***

Biopharmaceutics Assessment

1. **Background**

   Vasostrict ® (API: Vasopressin) is a polypeptide hormone that causes contraction of vascular and other smooth muscles and antidiuresis. This product is approved under NDA-204485 for the use of increasing blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines. The current approved formulation presentations are the 20 units/mL (single use) and 200 units/10 mL (multiple use) vials. The diluent for Vasostrict® can be either saline (0.9% sodium chloride) or 5% dextrose in water (D5W). The Applicant states that the current approved presentations require dilution prior to use for intravenous (iv) administration, whereas the proposed product of 40 units/100 mL and 60 units/100 mL is a premixed solution that does not require further dilution.

2. **Bridging of Vasostrict ® (Vasopressin injection, USP) approved and proposed drug products**

   The route of administration, dosage form, and indication for the proposed and listed drug products are the same. A side-by-side comparison of the composition of the proposed drug product and listed drug is shown in Table 2 (Appendix). The Applicant provided bridging information/data in response to the IR letter (Appendix). The response from Applicant is acceptable (The detail review assessment is in Appendix).

3. **Recommendation**

   In summary, the Applicant has adequately bridged the proposed premixed presentations (40 units/100 mL and 60 units/100 mL) of Vasostrict® to currently approved drug product presentations (20 units/mL and 200 units/10 mL).

Appendix

Information Request Sent to the Applicant (dated 02/13/2020)

The formulation of proposed drug product is not qualitatively and quantitatively the same as the formulation of the designated listed drug product. (b) (4) (b) (4) However, a "bridge" between the proposed and the listed drug product may be supported by required information, based on 21 CFR 320.24(b)(6), that justifies the differences in drug products would not contribute to differences in the in vivo performance. The Agency recommends you submit the following additional information in support of the bridging under CFR 320.24(b)(6):

(1) Information that indicates whether the difference in inactive ingredients might affect the distribution or elimination of drug substance in vivo.
(2) Comparative physicochemical data (such as pH, osmolality, viscosity, specific gravity, color and clarity) for at least 3 production lots of the proposed drug product and 3 lots of the listed drug product. The measurements should be done in triplicate for each lot tested. The Agency suggests you include justification for why you believe that any observed differences in the physicochemical properties of the test and reference drug products would not impact the efficacy and safety of the proposed drug product

The Applicant responded to the above request on 02/21/2020.[2] Specifically, the Applicant updated Section 3.2.P.1.

(1) Information that indicates whether the difference in inactive ingredients might affect the distribution or elimination of drug substance in vivo.

Applicant's Response

The Applicant provided side-by-side comparison of the composition of the proposed drug product and the listed drug (Table 2), and states that both drugs have qualitatively the same inactive ingredients following (b) (4) *with the exception of* (b) (4) *Moreover, there are minor differences in the amount of* (b) (4) *in the proposed premixed products in comparison to the current approved strengths of 20 units/1 mL and 200 units/10 mL presentations following dilution.*

The (b) (4) *The Vasostrict® 40 units/100 mL and 60 units/100 mL presentations are adjusted to pH 3.8* (b) (4) *This standard is agreeable with the pH stated in USP monograph for Vasopressin Injection (pH 2.5-4.5).* (b) (4) (b) (4) *prior to administration. Once administered, IV solution are rapidly diluted in the systemic circulation, wherein pH*

[2] \\cdsesub1\evsprod\nda204485\0105\m1\us\complete-response.pdf

is maintained by the buffering capacity of the blood. (b) (4)

It is also noted that the amount of (b) (4) *included in the proposed premixed formulation* (b) (4) *is within the range* (b) (4) *of that administered to patients when the approved formulation is prepared (i.e., diluted) (Table 1). Therefore, the proposed product will not result in any difference in the distribution or elimination of vasopressin, as compared to the approved product.*

Table 2. Comparative compositions of the Proposed Vasostrict® Premixed Solution, 40 units/100 mL and 60 units/100 mL, versus the Listed Drug (Pre- and Post- dilution)

Ingredient	Function	Composition (per mL)				
		Listed Drug Pre-dilution		Listed Drug Post-dilution in D5W[a]	Proposed Premixed Solution	
		20 units / 1 mL single dose vial	200 units / 10 mL multiple dose vial	20 units / 1 mL single dose vial or 200 units / 10 mL multiple dose vial	40 units / 100 mL	60 units / 100 mL
Vasopressin, USP	API	20 units	20 units	0.1-1 units[b]	0.4 units	0.6 units
Dextrose Anhydrous, (b) (4)	(b) (4)	(b) (4)				
Acetic Acid (b) (4)						
Sodium Acetate (b) (4)						
Sodium Hydroxide, (b) (4)	pH adjusting agent					
Hydrochloric Acid,	pH adjusting agent					
Chlorobutanol, NF	Preservative					
Water for Injection, USP (b) (4)	(b) (4)					

(b) (4)

(b) (4)

Regarding to dextrose anhydrous, the amount of this inactive ingredient is very similar between the proposed premixed presentation (b) (4) *and the approved presentation following its dilution in D5W (Table 2). Specifically, When the approved formulation is diluted in D5W* (b) (4) (b) (4) *as labeled instruction (2.5mL Vasostrict® in 500mL and 5 mL Vasostrict® in 100 mL), it will result in dextrose content of* (b) (4) *in the proposed presentation. The dextrose anhydrous in the proposed premixed formulation is a* (b) (4) (b) (4) (b) (4) *Vasostrict® Premixed Solution 40 units/100 mL and 60 units/100 mL is in controlled range of* (b) (4) *which is appropriate for an iv injection* (b) (4) (b) (4) *Hence, the very minor difference of dextrose anhydrous content will not have impact on distribution or elimination of vasopressin in vivo.*

Reviewer's Assessment

The Applicant's response comparing qualitative and quantitative composition adequately bridges the proposed and approved presentations.

(2) Comparative physicochemical data (such as pH, osmolality, viscosity, specific gravity, color and clarity) for at least 3 production lots of the proposed drug product and 3 lots of the listed drug product. The measurements should be done in triplicate for each lot tested. The Agency suggests you include justification for why you believe that any observed differences in the physicochemical properties of the test and reference drug products would not impact the efficacy and safety of the proposed drug product

Applicant's Response

The results of the test on physiochemical properties, including pH, osmolarity, viscosity, specific gravity, color, and clarity on three product lots of the proposed drug product and three lots of the approved drug product (all lots were conducted in triplicate) are shown in Table 3 and 4. It is noted that the premixed proposed drug product contain dextrose, the approved drug product was therefore diluted in D5W before testing.

Table 3: Physicochemical Properties of Vasostrict 20 units/mL SDV and Vasostrict 20 unit/mL MDV diluted to 0.6 units/mL with D5W, and Vasostrict Pre-mix 0.6 units/mL

Sample	Lot	Preparation	pH	Osmolality (mOsm/kg)	Viscosity (cP @ 25 °C)	Specific Gravity (25 °C)	Color and Clarity[1]
Vasostrict® 20 unit/mL, 1 mL single dose vial Diluted with D5W to 0.6 unit/mL	343736	Sample 1	(b) (4)				
		Sample 2					
		Sample 3					
	343737	Sample 1					
		Sample 2					
		Sample 3					
	343739	Sample 1					
		Sample 2					
		Sample 3					
Vasostrict® 20 unit/mL, 10 mL multiple dose vial Diluted with D5W to 0.6 unit/mL	319160	Sample 1					
		Sample 2					
		Sample 3					
	335148	Sample 1					
		Sample 2					
		Sample 3					
	343528	Sample 1					
		Sample 2					
		Sample 3					
Vasostrict® Pre-mix 0.6 unit/mL	313654	Sample 1					
		Sample 2					
		Sample 3					
	313655	Sample 1					
		Sample 2					
		Sample 3					
	313656	Sample 1					
		Sample 2					
		Sample 3					

Raw data: recorded in Notebook 2687 – pg 1 to 14, and Notebook 2688 – pg 1 to 21.

(b) (4)

Table 4: Physicochemical Properties of Vasostrict 20 units/mL SDV and Vasostrict 20 units/mL MDV diluted to 0.4 units/mL with D5W, and Vasostrict Pre-mix 0.4 units/mL

Sample	Lot	Sample	pH	Osmolality (mOsm/kg)	Viscosity (cP @ 25 °C)	Specific Gravity (25 °C)	Color and Clarity[1]
Vasostrict® 20 unit/mL, 1 mL single dose vial Diluted with D5W to 0.4 unit/mL	343736	Sample 1	(b) (4)				
		Sample 2					
		Sample 3					
	343737	Sample 1					
		Sample 2					
		Sample 3					
	343739	Sample 1					
		Sample 2					
		Sample 3					
Vasostrict® 20 unit/mL, 10 mL multiple dose vial Diluted with D5W to 0.4 unit/mL	319160	Sample 1					
		Sample 2					
		Sample 3					
	335148	Sample 1					
		Sample 2					
		Sample 3					
	343528	Sample 1					
		Sample 2					
		Sample 3					
Vasostrict® Pre-mix 0.4 unit/mL	313661	Sample 1					
		Sample 2					
		Sample 3					
	313662	Sample 1					
		Sample 2					
		Sample 3					
	338603	Sample 1					
		Sample 2					
		Sample 3					

Raw data: recorded in Notebook 2687 – pg 1 to 14, and Notebook 2688 – pg 1 to 21.

(b) (4)

It is noted that there is small difference in pH between the approved and the propsoed drug product. The differnece is about (b) (4) pH units across the samples. According to USP D5W injection pH specification is 3.2-6.5 while the pH range of proposed drug product is (b) (4) which is acceptable range.

Overall, the physocochemical data between the listed drug and proposed drug product are comparable. Therefore, there is no impact on safety and efficacy of the drug product.

Reviewer's Assessment

Physicochemical properties of the proposed and approved presentations of Vasostrict® are comparable. The Applicant's response comparing physicochemical properties adequately bridges the proposed and approved presentations.

Huong Moldthan

Digitally signed by Huong Moldthan
Date: 3/24/2020 01:14:48PM
GUID: 5ae328d00016b322ad761cc7bf7f0978

Poonam Delvadia

Digitally signed by Poonam Delvadia
Date: 3/24/2020 01:44:11PM
GUID: 5388edae000671a12787e2fcf4cde1bb

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204485Orig1s013

OTHER REVIEW(S)

REGULATORY BUSINESS PROCESS MANAGER LABELING REVIEW

Office of Program and Regulatory Operations

Application: 204485/S-013

Name of Drug: Vasostrict (vasopressin injection, USP) 40 units/100 mL and 60 units/100 mL

Applicant: Par Sterile Products, LLC

Contact information: Katharine Nowalski Manager, Regulatory Affairs
Phone: (248) 656-5282 Fax: (845) 573-5796 Email: katharine.nowalski@parpharm.com

Submission and amendment receipt date: 12/20/2019; 2/6/2020, 2/21/2020, 3/6/2020, 3/20/2020, and 4/4/2020

Material Reviewed:

Material	Submit Date	Receipt Date	Compared to
Carton/container	3/20/2020	3/20/2020	Approved C/C label S-004 on 12/17/2016
Prescribing information	3/20/2020	3/20/2020	Approved PI S-014 on 2/21/2020

Background and Summary Description:

Par Sterile Products, LLC submitted on 12/20/2019, Prior Approval Supplement seeking approval of a 40 units/100 mL and a 60 units/100 mL single dose vial presentations for the same indication, route of administration and dosage form as the currently approved Vasostrict presentations. The proposed single dose presentations will allow for immediate use of the finished product without the need for further dilution prior to administration (premixed). DMEPA was consulted 12/26/2019. DMEPA IR sent to applicant 2/14/2020, and received 3/6/2020. DMEPA's first review completed 3/16/2020, with additional comments that were sent to the applicant on 3/17/2020. Applicant responded 3/20/20 and DMEPA completed final review 3/25/20. Labeling acceptable by DMEPA reviewer (Grace Jones) on 3/25/20, and CMC reviewer, Kris Raman on 4/11/20.

Review

This comparison was done by visually comparing the proposed to the last submitted or approved labeling on file.

The following are the assessments for each change identified:

Prescribing Information
The highlights indicate the differences/update to the PI
HIGHLIGHTS OF PRESCRIBING INFORMATION

Before

----------DOSAGE AND ADMINISTRATION----------

• Dilute Vasostrict® with normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) to either 0.1 units/mL or 1 unit/mL for intravenous administration. Discard unused diluted solution after 18 hours at room temperature or 24 hours under refrigeration. (2.1)

After(Submitted 3/20/20)

----------DOSAGE AND ADMINISTRATION----------

• Dilute 20 units/mL single dose vial or 200 units/10 mL (20 units/mL) multiple dose vial contents with normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) to either 0.1 units/mL or 1 unit/mL for intravenous administration. Discard unused diluted solution after 18 hours at room temperature or 24 hours under refrigeration. (2.1)

• The 40 units/100 mL and 60 units/100 mL single dose vials do not require further dilution prior to administration. (2.1 (b) (4)

Comment: Changes highlighted acceptable by DMEPA and CMC reviewers

Before

----------DOSAGE FORMS AND STRENGTHS----------

• Injection: 20 units per mL (3)

After(Submitted 3/20/20)

----------DOSAGE FORMS AND STRENGTHS----------

• Injection: 20 units/mL in a single dose vial and 200 units/10 mL (20 units/mL) in a multiple dose vial. To be used after dilution. (3) 40 units/100 mL (0.4 units/mL) and 60 units/100 mL (0.6 units/mL) in single dose vials. Ready to use. (3)

Comment: Changes highlighted acceptable by DMEPA and CMC reviewers

Before

Revised: 02/2020
After(Submitted 3/20/20)
Revised: 03/2020

Comment: Changes highlighted acceptable by DMEPA and CMC reviewers

FULL PRESCRIBING INFORMATION: CONTENTS*

Before
2 DOSAGE AND ADMINISTRATION
2.1 Preparation of Diluted Solutions

After(Submitted 3/20/20)
2 DOSAGE AND ADMINISTRATION
2.1 Preparation of Solution

Comment: Changes highlighted acceptable by DMEPA and CMC reviewers

FULL PRESCRIBING INFORMATION

2 DOSAGE AND ADMINISTRATION
Before
2.1 Preparation of Diluted Solutions
Dilute Vasostrict® in normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W) prior to use for intravenous administration. Discard unused diluted solution after 18 hours at room temperature or 24 hours under refrigeration.

TABLE here but no changes

Inspect parenteral drug products for particulate matter and discoloration prior to use, whenever solution and container permit.

After (Submitted 3/20/20)
2.1 Preparation of Solution
Inspect parenteral drug products for particulate matter and discoloration prior to use, whenever solution and container permit.
Vasostrict® Solution for Dilution:, 20 units/mL in a single dose vial and 200 units/10 mL (20 units/mL)
TABLE here but no changes

Vasostrict® Premixed Solution:, 40 units/100 mL (0.4 units/mL) and 60 units/100 mL (0.6 units/mL)
This product does not require further dilution prior to administration.

Comment: Changes highlighted acceptable by DMEPA and CMC reviewers

3 DOSAGE FORMS AND STRENGTHS

Before
Vasostrict® (vasopressin injection, USP) is a clear, practically colorless solution for intravenous administration available as 20 units/mL in a single dose vial and 200 units/10 mL (20 units/mL) in a multiple dose vial.

After (Submitted 3/20/20)
Vasostrict® (vasopressin injection, USP) is a clear, practically colorless solution for intravenous administration available as 20 units/mL in a single dose vial and 200 units/10 mL (20 units/mL) in a multiple dose vial. To be used after dilution.

Vasostrict® is also available premixed as 40 units/100 mL (0.4 units/mL) and 60 units/100 mL (0.6 units/mL) in single dose vials. Ready to use.

Comment: Changes highlighted acceptable by DMEPA and CMC reviewers

11 DESCRIPTION

Before
Vasopressin is a polypeptide hormone that causes contraction of vascular and other smooth muscles and antidiuresis. Vasostrict® is a sterile, aqueous solution of synthetic arginine vasopressin for intravenous administration. The 1 mL solution contains vasopressin 20 units/mL, Water for Injection, USP, and sodium acetate buffer adjusted to a pH of 3.8. The 10 mL solution contains vasopressin 20 units/mL, chlorobutanol, NF 0.5% as a preservative, and Water for Injection, USP and, sodium acetate buffer adjusted to a pH of 3.8.

After(Submitted 3/20/20)

The 1 mL solution contains vasopressin 20 units/mL, Water for Injection, USP, and sodium acetate buffer adjusted to a pH of 3.8. The 10 mL solution contains vasopressin 20 units/mL, chlorobutanol, NF 0.5% as a preservative, (b) (4) Water for Injection, USP and (b) (4) sodium acetate buffer adjusted to a pH of 3.8.

The 100 mL solution contains vasopressin 0.4 units/mL or 0.6 units/mL. Each mL of the 0.4 unit/mL strength also contains dextrose anhydrous, acetic acid, sodium acetate and Water for

Injection, USP. Each mL of the 0.6 unit/mL strength also contains dextrose anhydrous, acetic acid, sodium acetate and Water for Injection, USP. Sodium hydroxide and hydrochloric acid are included to adjust to a pH of 3.8.

Comment: Changes highlighted acceptable by DMEPA and CMC reviewers

16 HOW SUPPLIED/STORAGE AND HANDLING

Before

Vasostrict® (vasopressin injection, USP) is a clear, practically colorless solution for intravenous administration available as:
NDC 42023-164-25: A carton of 25 single dose vials each containing vasopressin 1 mL at 20 units/mL.
NDC 42023-190-01: A carton of 1 multiple dose vial containing vasopressin 10 mL at 200 units/10 mL (20 units/mL).

	Unopened Refrigerated 2°C to 8°C (36°F to 46°F)	Unopened Room Temperature 20°C to 25°C (68°F to 77°F) Do not store above 25°C (77°F)	Opened (After First Puncture
1 mL Vial	Until manufacturer expiration date	12 months or until manufacturer expiration date, whichever is earlier	N/A
10 mL Vial	Until manufacturer expiration date	12 months or until manufacturer expiration date, whichever is earlier	30 days

After (Submitted 3/20/20)
Vasostrict® (vasopressin injection, USP) is a clear, practically colorless solution for intravenous administration available as:
NDC 42023-164-25: A carton of 25 single dose vials each containing vasopressin 1 mL at 20 units/mL.
NDC 42023-190-01: A carton of 1 multiple dose vial containing vasopressin 10 mL at 200 units/10 mL (20 units/mL).
NDC 42023-219-10 (b) (4): A carton of 10 single dose vials (b) (4) vasopressin 100 mL at 40 units/100 mL (0.4 units/mL).

NDC 42023-220-10 (b) (4): A carton of 10 single dose vials (b) (4) vasopressin 100 mL at 60 units/100 mL (0.6 units/mL). Store between 2°C and 8°C (36°F and 46°F). Do not freeze.

	Unopened Refrigerated 2°C to 8°C (36°F to 46°F)	Unopened Room Temperature 20°C to 25°C (68°F to 77°F) Do not store above 25°C (77°F)	Opened (After First Puncture)
	Until manufacturer expiration date	12 months or until manufacturer expiration date, whichever is earlier	N/A
	Until manufacturer expiration date	12 months or until manufacturer expiration date, whichever is earlier	30 days
100 mL Vial	Until manufacturer expiration date	12 months or until manufacturer expiration date, whichever is earlier	N/A

Comment: Changes highlighted acceptable by DMEPA and CMC reviewers

Before

R02/20 OS164J-01-90-XX

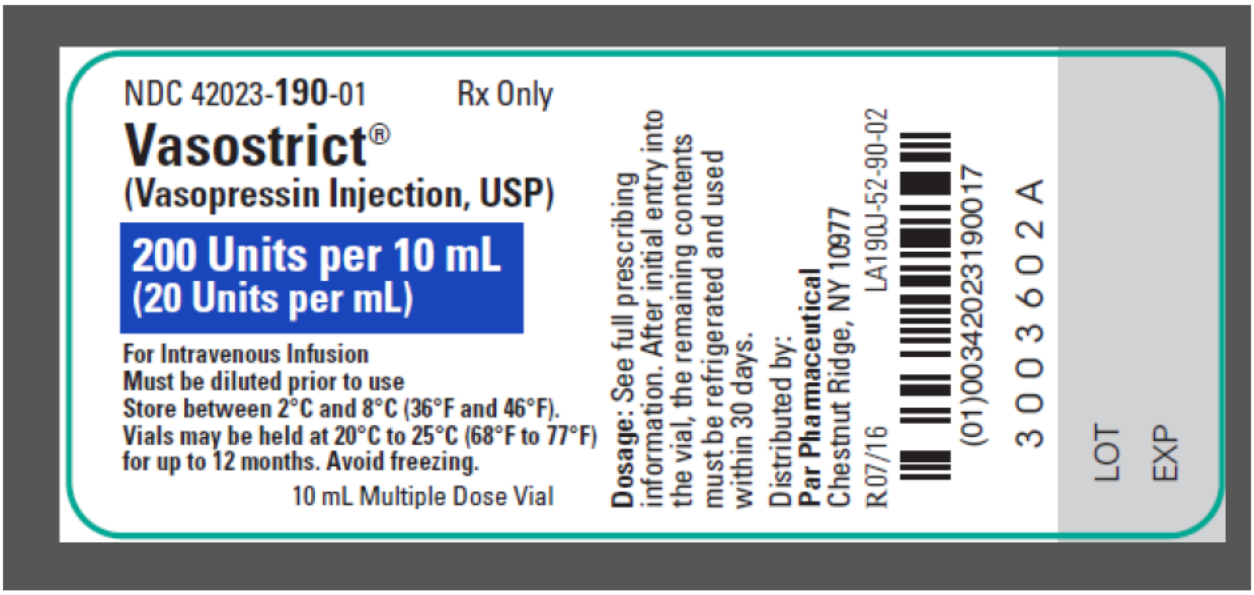
After(Submitted 3/20/20)

R03/20 OS164J-01- 90-XX

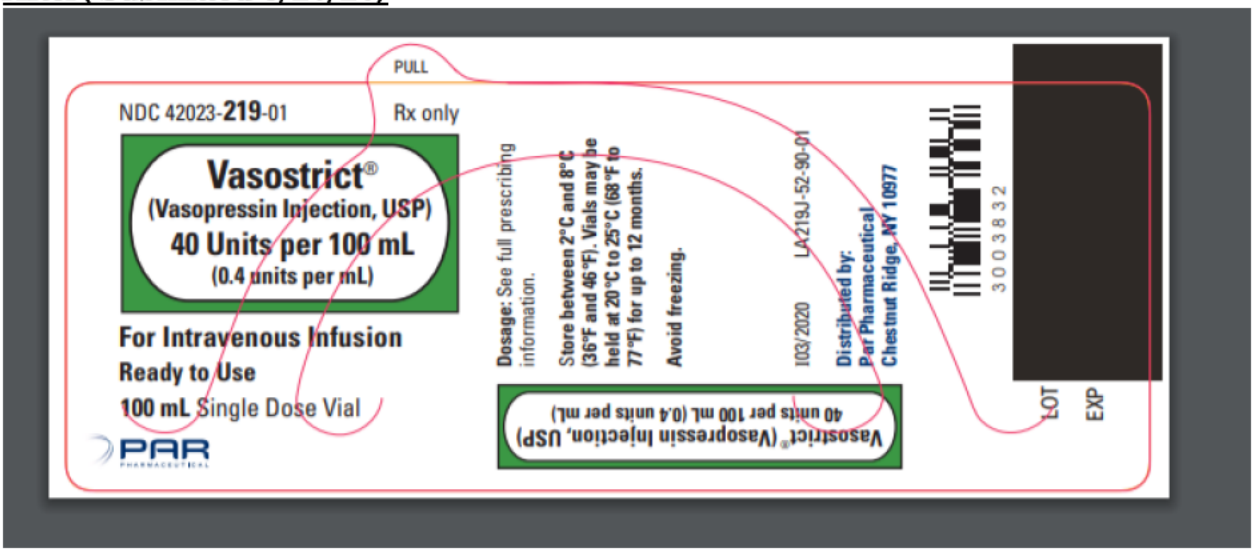
Comment: Changes highlighted acceptable by DMEPA and CMC reviewers

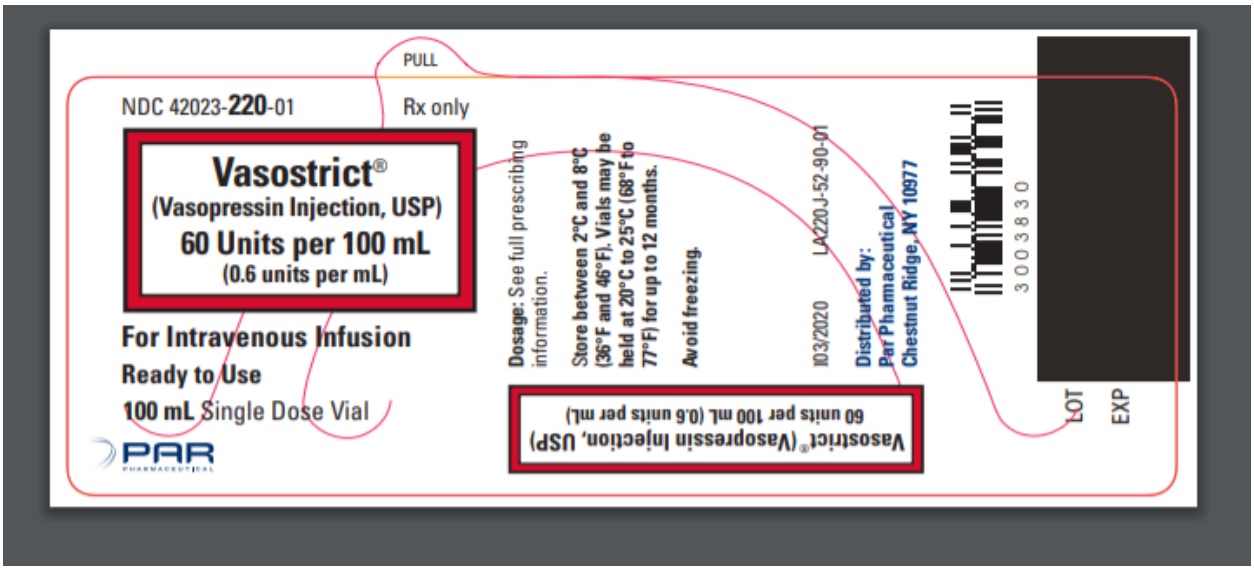
Carton/Container

Before



After(Submitted 3/20/20)





The following are updates to the new C/C labels

- Layout of new carton/container label updated
- Must be diluted prior to use removed and updated with "Ready to use "
- The following statement removed from the new packaging-"After initial entry into the vial, the remaining contents must be refrigerated and used within 30 days"
- Additional display of drug proprietary name, established name and strength included in a box is displayed upside down on the side panel
- PAR pharmaceuticals logo displayed bottom of front panel

Comment: Changes acceptable by DMEPA and CMC reviewers

Recommendations

The changes to content of labeling and immediate container labels are acceptable. The supplement is recommended for approval.

Abolade (Bola) Adeolu 4/14/2020

RBPM Name Date

Regulatory Business Process Manager
Office of Programs and Regulatory Operations
Office of Pharmaceutical Quality

{See appended electronic signature page}

Teicher Agosto 4/14/2020

Secondary/QAL Name Date

Regulatory Business Process Manager
Office of Programs and Regulatory Operations
Office of Pharmaceutical Quality

{See appended electronic signature page}

Abolade Adeolu

Digitally signed by Abolade Adeolu
Date: 4/15/2020 03:50:00PM
GUID: 508da6ea000275025a9caf8705a0d70e

Teicher Agosto

Digitally signed by Teicher Agosto
Date: 4/15/2020 04:05:15PM
GUID: 525da15600038cc367b38199be1ab383

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	March 25, 2020
Requesting Office or Division:	Office of Pharmaceutical Quality (OPQ)
Application Type and Number:	NDA 204485/S-013
Product Name and Strength:	Vasostrict (vasopressin) injection, 40 units per 100 mL (0.4 units per mL), and 60 units per 100 mL (0.6 units per mL)
Applicant/Sponsor Name:	PAR Sterile Products LLC (PAR)
OSE RCM #:	2019-2653-1
DMEPA Safety Evaluator:	Grace P. Jones, PharmD, BCPS
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and Prescribing Information (PI) received on March 23, 2020 for Vasostrict. Office of Pharmaceutical Quality (OPQ) requested that we review the revised container labels for Vasostrict (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

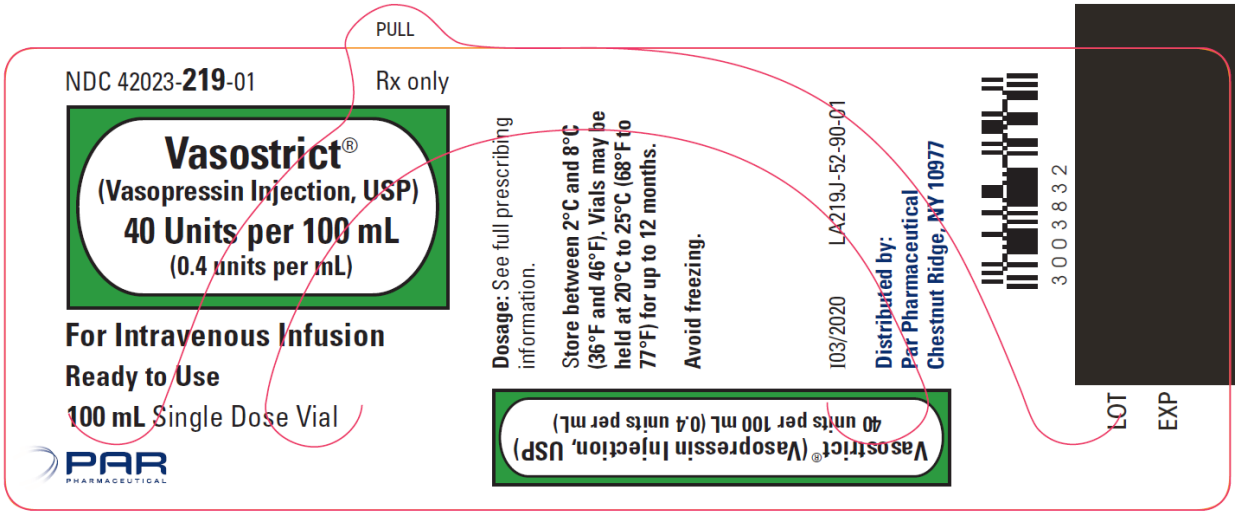
The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] Jones G. Label and Labeling Review for Vasostrict (NDA 204485/S-013). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 MAR 16. RCM No.: 2019-2653.

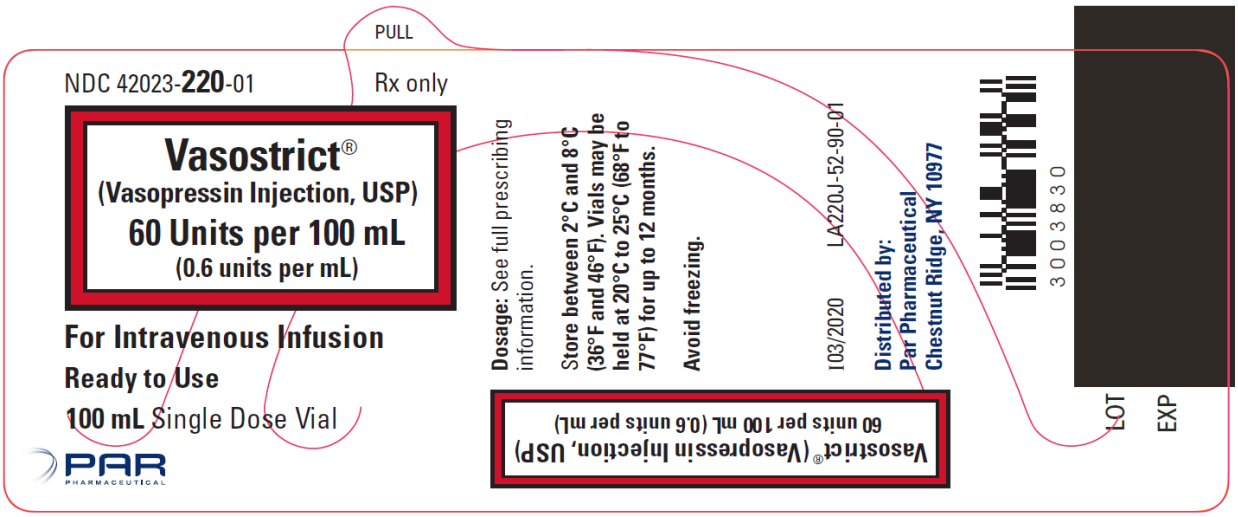
APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MARCH 23, 2020

Container labels

40 units/100 mL



60 units/100 mL



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/

GRACE JONES
03/25/2020 10:45:28 AM

CHI-MING TU
03/25/2020 11:32:18 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 16, 2020
Requesting Office or Division:	Office of Pharmaceutical Quality (OPQ)
Application Type and Number:	NDA 204485/S-013
Product Name, Dosage Form, and Strength:	Vasostrict (vasopressin) injection, 40 units per 100 mL (0.4 units per mL), and 60 units per 100 mL (0.6 units per mL)
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	PAR Sterile Products LLC (PAR)
FDA Received Date:	December 20, 2019
OSE RCM #:	2019-2653
DMEPA Safety Evaluator:	Grace P. Jones, PharmD, BCPS
DMEPA Team Leader:	Chi-Ming (Alice) Tu, PharmD, BCPS

1 REASON FOR REVIEW

PAR submitted NDA 204485/Supplement-013 on December 20, 2019 for Vasostrict (vasopressin) injection seeking approval for a 40 units/100 mL and 60 units/100 mL single dose vial presentations for the same indication, route of administration, and dosage form as the currently approved Vasostrict.

The currently approved Vasostrict 20 units/mL vial and 200 units/10 mL (20 units per mL) vial presentations must be diluted prior to use for intravenous administration. The proposed 40 units/100 mL and 60 units/100 mL single dose vial presentations do not require dilution before administration.

OPQ requested that we review the proposed container labels, carton labeling, and Prescribing Information (PI) for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C (N/A)
ISMP Newsletters*	D (N/A)
FDA Adverse Event Reporting System (FAERS)*	E (N/A)
Other	F (N/A)
Labels and Labeling	G

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed the proposed Vasostrict container labels, carton labeling, and Prescribing Information (PI).

The currently approved Vasostrict 20 units/mL vial and 200 units/10 mL (20 units per mL) vial presentations must be diluted with 0.9% sodium chloride or 5% dextrose in water to either 0.1 unit/mL or 1 unit/mL concentrations prior to intravenous administration. The proposed 40 units/100 mL and 60 units/100 mL single dose vial presentations are ready to infuse at 0.4 units/mL and 0.6 units/mL concentrations, respectively. We note this difference in

concentrations of the drug at the time of administration, 0.4 units/mL and 0.6 units/mL for the proposed vial presentations and 0.1 units/mL or 1 unit/mL for the currently marketed Vasostrict (after dilution). Thus, we sent PAR an information request (IR) to provide rationale for the differences in concentration for the proposed ready to use vial presentations from the currently marketed product.

PAR stated in its response that "alternative concentrations of diluted Vasostrict may be prepared" and that the proposed ready to use presentations "have been identified through market intelligence as those commonly prepared for use in hospital setting." Because the 0.4 units/mL and 0.6 units/mL concentrations are already being used in the usual clinical setting (they are only new concentrations in term of being manufactured by drug applicants), we do not anticipate the proposed 0.4 units/mL and 0.6 units/mL concentration products to introduce any new risk of concentration confusion medication errors. Based on PAR's response and our analysis, we find the proposed 0.4 units/mL and 0.6 units/mL concentrations reasonable for the proposed 40 units/100 mL and 60 units/100 mL single dose vial presentations.[a]

We note that the proposed container labels and carton labeling are differentiated in color and graphic design from the currently approved Vasostrict 20 units/mL and 200 units/10 mL vials. Moreover, the proposed Vasostrict container labels and carton labeling contain a graphic green box and a red box around the product name for the 40 units/100 mL and 60 units/100 mL vials, respectively, that provides differentiation between the proposed presentations and the currently approved presentations.

We identified areas in the proposed Vasostrict PI and container labels that may be improved for clarity to minimize potential medication errors.

4 CONCLUSION & RECOMMENDATIONS

The proposed Vasostrict PI and container labels may be improved for clarity. We provide specific recommendations in Section 4.1 and Section 4.2.

4.1 RECOMMENDATIONS FOR OFFICE OF PHARMACEUTICAL QUALITY (OPQ)

A. Prescribing Information

1. How Supplied/Storage and Handling Section

a. To ensure consistency in Section 16 How Supplied of the PI, revise the statement "A carton of 10 single dose vials (b) (4) vasopressin 100 mL at 40 units/100 mL (0.4 units/mL)" to read, "A carton of 10 single-dose vials. Each vial contains vasopressin 100 mL at 40 units/100 mL (0.4

[a] Response to Information Request for Vasostrict (NDA 204485/S-013). Chestnut Ridge (NY): Par Sterile Products, LLC. 2020 FEB 21. Available from: \\cdsesub1\evsprod\nda204485\0105\m1\us\complete-response.pdf

units/mL)". Similarly, also add the word "Each vial" to the statement for the 60 units/100 mL presentation.

4.2 RECOMMENDATIONS FOR PAR STERILE PRODUCTS LLC

We recommend the following be implemented prior to approval of this NDA Supplement:

A. Container Labels

1. We note that the inverted box containing the product name on the proposed container labels for Vasostrict 40 units/100 mL and 60 units/100 mL vials would appear upright when the "pull" handle is used for hanging the product during administration. For consistency and to improve the visibility of the product name in this inverted box, we recommend using the same colored box format, (i.e., green box for the 40 units/100 mL vial and red box for the 60 units/100 mL vial) also for the inverted box, as space permits.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Vasostrict received on December 20, 2019 from PAR Sterile Products LLC.

Table 2. Relevant Product Information for Vasostrict	
Initial Approval Date	April 17, 2014
Active Ingredient	vasopressin
Indication	To increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines.
Route of Administration	Intravenous
Dosage Form	injection
Strength	Currently approved: • 20 units per mL • 200 units per 10 mL (20 units per mL) *Proposed:* • 40 units/100 mL (0.4 units/mL) • 60 units/100 mL (0.6 units/mL)
Dose and Frequency	For post-cardiotomy shock, start with a dose of 0.03 units/minute. For septic shock, start with a dose of 0.01 units/minute. If the target blood pressure response is not achieved, titrate up by 0.005 units/minute at 10- to 15-minute intervals. The maximum dose for post-cardiotomy shock is 0.1 units/minute and for septic shock 0.07 units/minute. After target blood pressure has been maintained for 8 hours without the use of catecholamines, taper Vasostrict by 0.005 units/minute every hour as tolerated to maintain target blood pressure.
How Supplied	• carton of 25 single dose vials each containing vasopressin 1 mL at 20 units/mL • carton of 1 multiple dose vial containing vasopressin 10 mL at 200 units/10 mL (20 units/mL) • carton of 10 single dose vials containing vasopressin 100 mL at 40 units/100 mL (0.4 units/mL) • carton of 10 single dose vials containing vasopressin 100 mL at 60 units/100 mL (0.6 units/mL).

Storage	Store between 2°C and 8°C (36°F and 46°F). Do not freeze. Vials may be held up to 12 months upon removal from refrigeration to room temperature storage conditions (20°C to 25°C [68°F to 77°F], USP Controlled Room Temperature), anytime within the labeled shelf life. Once removed from refrigeration, unopened vial should be marked to indicate the revised 12 month expiration date. If the manufacturer's original expiration date is shorter than the revised expiration date, then the shorter date must be used. Do not use Vasostrict® beyond the manufacturer's expiration date stamped on the vial. After initial entry into the 10 mL vial, the remaining contents must be refrigerated. Discard the refrigerated 10 mL vial after 30 days after first puncture.
Container Closure	Currently approved: • Vial, 10 mL (b) (4) • Stopper, (b) (4) • Cap, (b) (4) *Proposed:* • Vial, 100 mL, (b) (4) • Stopper, (b) (4) • (b) (4) Stopper

APPENDIX B. PREVIOUS DMEPA REVIEWS

On January 29, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Vasostrict and NDA 204485. Our search identified 9 previous reviews[b,c,d,e,f,g,h,i,j], and we confirmed that our previous recommendations were implemented or considered.

[b] Thomas S. Label and Labeling Memo for Vasostrict (NDA 204485/S-004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 DEC 15. OSE RCM No.: 2016-2236-1.

[c] Thomas S. Label and Labeling Memo for Vasostrict (NDA 204485/S-004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 OCT 25. OSE RCM No.: 2016-2236.

[d] Thomas S. Label and Labeling Review for Vasostrict (NDA 204485/S-004). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 JUN 22. OSE RCM No.: 2016-1060.

[e] Gao T. Label and Labeling Review for Vasostrict (NDA 204485/S-002). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2015 MARCH 27. OSE RCM No.: 2015-563.

[f] Stewart J. Label and Labeling Review for Vasostrict (NDA 204485/S-001). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 JULY 28. OSE RCM No.: 2014-1283.

[g] Stewart J. Label and Labeling Review Memo for Vasostrict (NDA 204485). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 APRIL 8. OSE RCM No.: 2013-2864-2.

[h] Stewart J. Label and Labeling Review Memo for Vasostrict (NDA 204485). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 FEB 26. OSE RCM No.: 2013-2864-1.

[i] Stewart J. Label and Labeling Review for Vasostrict (NDA 204485). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 FEB 12. OSE RCM No.: 2013-2864.

[j] DeFronzo K. Label, Labeling and Packaging Review for [redacted] (b) (4) (NDA 204485). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2013 JUNE 7. OSE RCM No.: 2012-2808.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[k] along with postmarket medication error data, we reviewed the following Vasostrict labels and labeling submitted by PAR Sterile Products LLC.

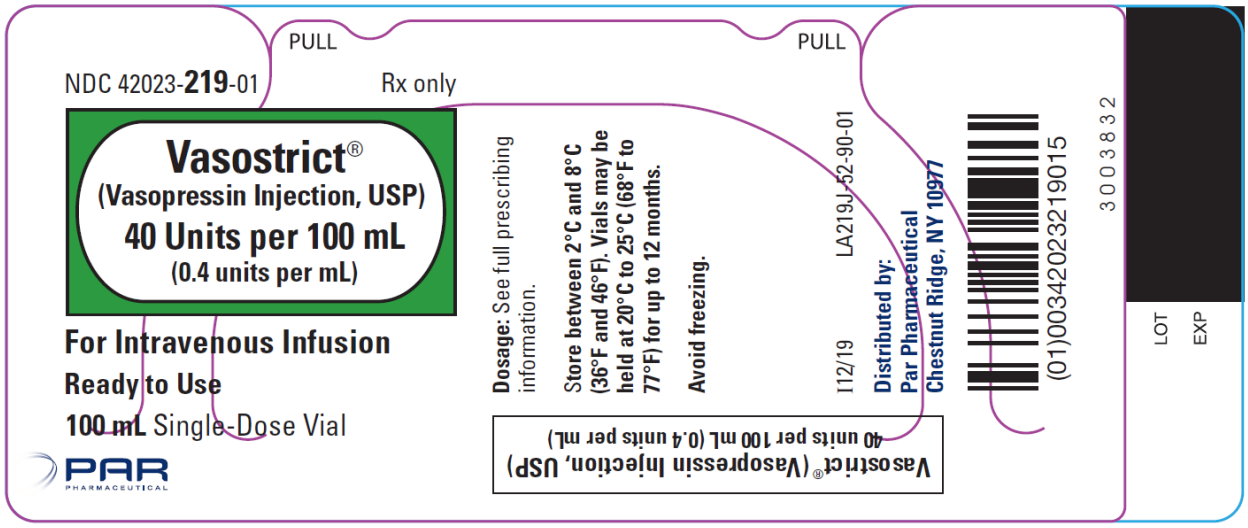
- Container labels received on December 20, 2019
- Carton labeling received on December 20, 2019
- Prescribing Information (Image not shown) received on December 20, 2019, available from:
    - Tracked Changes: \\cdsesub1\evsprod\nda204485\0083\m1\us\vasostrict-insert-tracked-changes.pdf
    - Clean: \\cdsesub1\evsprod\nda204485\0083\m1\us\vasostrict-insert-clean.doc

[k] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

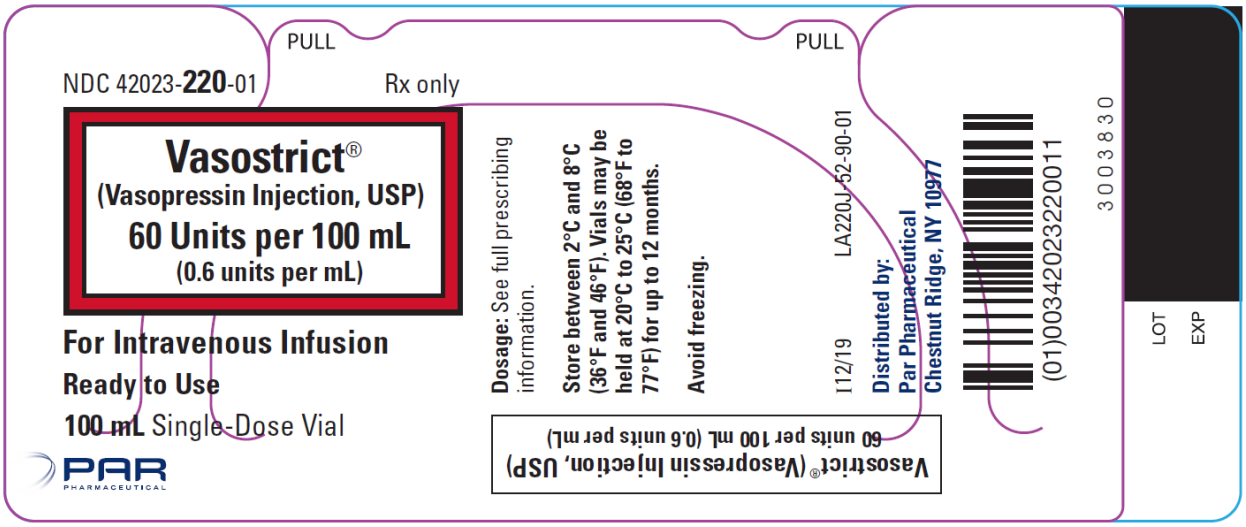
G.2 Label and Labeling Images

Container Labels

40 units/100 mL

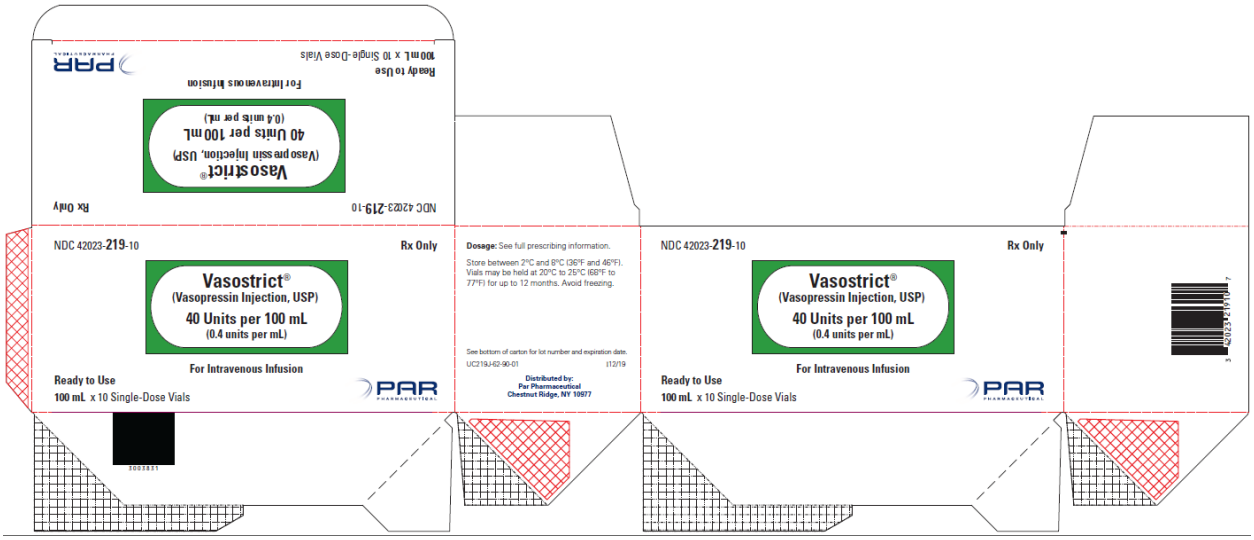


60 units/100 mL

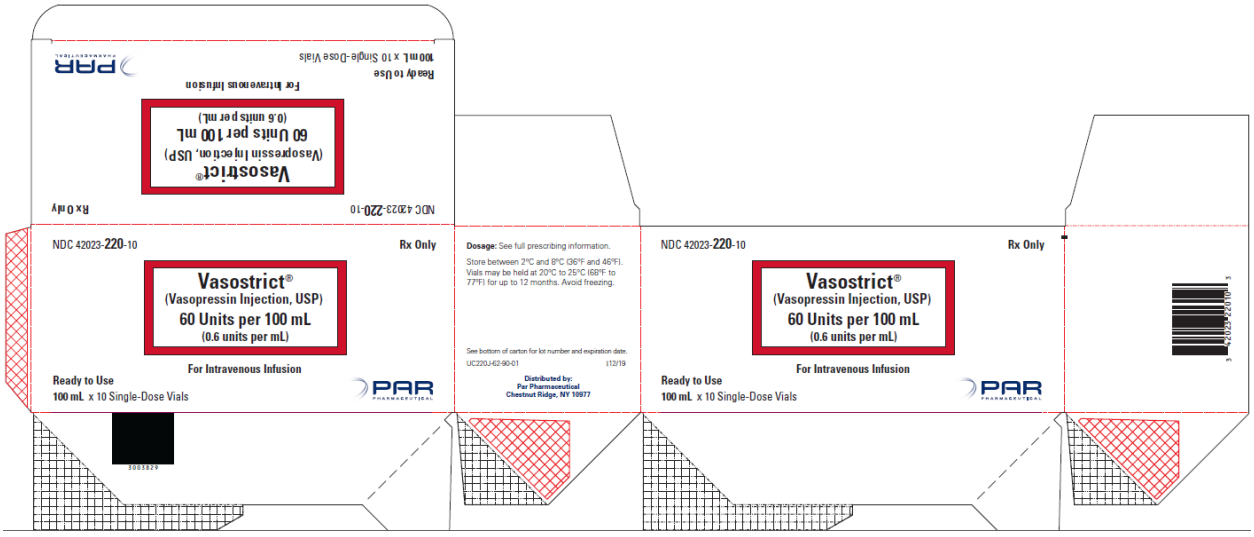


Carton Labeling

40 units/100 mL



60 units/100 mL



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/

GRACE JONES
03/16/2020 10:00:48 AM

CHI-MING TU
03/16/2020 12:12:29 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204485Orig1s013

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 204485/S-013

INFORMATION REQUEST

Par Sterile Products LLC
Attention: Katharine Nowalski, MS
Manager, Regulatory Affairs
Six Ram Ridge Road
Chestnut Ridge, NY 10977

Dear Ms. Nowalski:

Please refer to your supplemental New Drug Application (sNDA) dated December 20, 2019, received December 20, 2019, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vasostrict (Vasopressin) Injection.

We are reviewing the Process section of your submission and have the following comments and information requests. We request a prompt written response by April 6, 2020 in order to continue our evaluation of your supplemental NDA.

Comm

A. Pr

1.

2

If you
abolad

Sincerely,

{See appended electronic signature page}

Abolade (Bola) Adeolu
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Abolade Adeolu

Digitally signed by Abolade Adeolu
Date: 4/02/2020 11:37:21AM
GUID: 508da6ea000275025a9caf8705a0d70e

NDA 204485/S-013

INFORMATION REQUEST

Par Sterile Products LLC
Attention: Katharine Nowalski
Manager, Regulatory Affairs
Six Ram Ridge Road
Chestnut Ridge, NY 10977

Dear Ms. Nowalski:

Please refer to your supplemental New Drug Application (sNDA) dated December 20, 2019, received December 20, 2019, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vasostrict (Vasopressin) Injection.

We are reviewing the Biopharmaceutics section of your submission and have the following comments and information requests. We request a prompt written response by February 21, 2020 in order to continue our evaluation of your supplemental NDA.

Comments and information requests:

A. Biopharmaceutics

The formulation of proposed drug product is not qualitatively and quantitatively the same as the formulation of the designated listed drug product (b) (4) (b) (4) However, a "bridge" between the proposed and the listed drug product may be supported by required information, based on 21 CFR 320.24(b)(6), that justifies the differences in drug products would not contribute to differences in the in vivo performance. The Agency recommends you submit the following additional information in support of the bridging under CFR 320.24(b)(6):

(1) Information that indicates whether the difference in inactive ingredients might affect the distribution or elimination of drug substance in vivo.

(2) Comparative physicochemical data (such as pH, osmolality, viscosity, specific gravity, color and clarity) for at least 3 production lots of the proposed drug product and 3 lots of the listed drug product. The measurements should be done in triplicate for each lot tested. The Agency suggests you include justification for why you believe that any observed differences in the physicochemical properties of the test and reference drug products would not impact the efficacy and safety of the proposed drug product

If you have any questions, please contact me at (301) 796 - 4264 or abolade.adeolu@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Abolade (Bola) Adeolu
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Abolade Adeolu

Digitally signed by Abolade Adeolu
Date: 2/13/2020 03:49:04PM
GUID: 508da6ea000275025a9caf8705a0d70e

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO: Office of Biostatistics	FROM: Abolade (Bola) Adeolu, OPQ, Ext 6-4264

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1/8/2020		204485/S-013	CMC	12/20/2020

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Vasostrict			2/28/2020

NAME OF FIRM: Par Sterile Products LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:
Applicant is seeking approval of a 40 units/100 mL and a 60 units/100 mL single dose vial presentations for the same indication, route of administration and dosage form as the current approved Vasostrict presentations.
Please review the linear regression results for the stability data for the proposed shelf life under both refrigeration and controlled room temperature.

CMC Reviewer is Krishna Raman, Ext 6-1739

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check all that apply)
Abolade (Bola) Adeolu, Ext 6-4264	☒ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

06/18/2013

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/

ABOLADE ADEOLU
01/08/2020 02:11:43 PM

NDA 204485/S-013

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Par Sterile Products, LLC
Attention: Katharine Nowalski
Manager, Regulatory Affairs
Six Ram Ridge Road
Chestnut Ridge, NY 10977

Dear Ms. Nowalski:[1]

We have received your supplemental new drug application (sNDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER:	204485
SUPPLEMENT NUMBER:	013
PRODUCT NAME:	Vasostrict® (vasopressin injection, USP) 40 units/100 mL and 60 units/100 mL
DATE OF SUBMISSION:	December 20, 2019
DATE OF RECEIPT:	December 20, 2019

This supplemental application proposes the following change: Approval of a 40 units/100 mL, and a 60 units/100 mL single dose vial presentations for the same indication, route of administration and dosage form as our current approved Vasostrict presentations.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 18, 2020, in accordance with 21 CFR 314.101(a).

If the application is filed, the user fee goal date will be April 20, 2020.

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

If you have questions, call me, at (301) 796 - 4264.

Sincerely,

{See appended electronic signature page}

Abolade (Bola) Adeolu, RPh, MS, MBA
Regulatory Business Process Manager
Office of Process and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Abolade Adeolu

Digitally signed by Abolade Adeolu
Date: 1/08/2020 02:44:14PM
GUID: 508da6ea000275025a9caf8705a0d70e

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO: OND/DCaRP	FROM: Abolade (Bola) Adeolu, OPQ Ext 6-4264

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
1/7/2020		204485/S-013	CMC	12/20/2019

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE:
Vasostrict			3/15/2020

NAME OF FIRM: Par Sterile Products LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE / ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END-OF-PHASE 2a MEETING
- ☐ END-OF-PHASE 2 MEETING
- ☐ RESUBMISSION
- ☐ SAFETY / EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

- ☐ PRIORITY P NDA REVIEW
- ☐ END-OF-PHASE 2 MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER (SPECIFY BELOW):
- ☐ CHEMISTRY REVIEW
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS/////
- ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE 4 STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL - BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG SAFETY

- ☐ PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ NONCLINICAL

COMMENTS / SPECIAL INSTRUCTIONS:

Please review the tox assessment in the extractables and leachables reports (b) (4)-01455 and (b) (4)-01456.

SIGNATURE OF REQUESTOR	METHOD OF DELIVERY (Check all that apply)
Abolade (Bola) Adeolu, Ext 6-4264	☒ DARRTS ☐ EMAIL ☐ MAIL ☐ HAND
PRINTED NAME AND SIGNATURE OF RECEIVER	PRINTED NAME AND SIGNATURE OF DELIVERER

06/18/2013

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/

ABOLADE ADEOLU
01/07/2020 09:19:50 AM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADM NISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Mail: OSE

FROM: Abolade (Bola) Adeolu, OPQ, Ext 6-4264

DATE: 12/26/2019	IND NO.	NDA NO. 204485-SUPPL-13	TYPE OF DOCUMENT: CMC Labeling	DATE OF DOCUMENT: 12/20/2019

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE: 2/28/2020
Vasostrict® (vasopressin injection, USP) 40 units/100 mL and 60 units/100 mL			

NAME OF FIRM: Par Sterile Products, LLC

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ MEDICATION ERRORS
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:
Prior Approval Supplement seeking approval of a 40 units/100 mL and a 60 units/100 mL single dose vial presentations for the same indication, route of administration and dosage form as the current approved Vasostrict presentations.

Please review container labeling

SIGNATURE OF REQUESTER: Abolade (Bola) Adeolu, ext 6-4264	METHOD OF DELIVERY (Check all that apply) ☐ MAIL ■ DARRTS ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

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/

ABOLADE ADEOLU
12/26/2019 12:13:54 PM