CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212593Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 212593 ORIG-1-RESUB-25
(Vasopressin Injection)

Integrated Quality Review#2

Recommendation: Final Approval

Drug Name/Dosage Form	Vasopressin Injection
Strength	20 units/mL
Route of Administration	Intravenous Infusion
Rx/OTC Dispensed	Rx
Applicant	American Regent, Inc. (formerly Luitpold Pharmaceuticals, Inc.)
Submissions (s) Reviewed	NDA 212593 ORIG-1-RESUB-25

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Product	Dhanalakshmi Kasi	OPQ/ONDP/DNDPIII/NDPB5
Process and Facility	Upasana Sahu	OPQ/OPMA/DPMAIV/PMB12
RBPM	Grafton Adams	OPQ/OPRO/DRBPMI/RBPMB2
Application Technical Lead	Mohan Sapru	OPQ/ONDP/DNDPIII/NDPB5

Executive Summary

A. Quality Assessment Summary

Background: From the chemistry, manufacturing, and controls (CMC)/quality perspective, the original NDA 212593 (Vasopressin Injection) was recommended for approval (for details, refer to Integrated Quality Review; DARRTS, dated January 27, 2020). Because final approval of the NDA, under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)], could not be granted before expiration of a period of patent protection and/or exclusivity, the NDA was granted tentative approval on January 28, 2020 (for details, refer to CDTL Review, and Tentative Approval Letter; DARRTS, dated January 28, 2020).

Updated Stability Data: On June 4, 2020, the applicant, American Regent, Inc., submitted request that the FDA issue final approval for NDA 212593, and submitted Class1 resubmission to support stability/labeling updates. Based on the original NDA submission, a shelf-life of 24 months was approved for the product when stored at 2°C and 8°C (36°F and 46°F) in the proposed commercial container closure system. In the current Class1 resubmission, the applicant provided stability data to support the storage condition of 12 months at room temperature storage conditions (20 to 25°C [68 to 77°F], USP Controlled Room Temperature), in addition to 12 months at 2°C and 8°C (36°F and 46°F), to match the shelf-life of the Listed Drug, Vasostrict®. Evaluation of these stability data reveal that the product assay levels fall slightly while the levels of some impurities significantly increase at room temperature, but these changed levels are within the drug product stability specification limits.

Revised Label and Labeling: The updated stability data support the following label claim concerning product storage and handling:

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)
Until manufacturer expiration date	12 months or until manufacturer expiration date, whichever is earlier

Based on updated stability data, the applicant's revised container label and carton labeling and Prescribing Information (PI) are acceptable.

Assessment of Facilities: The drug substance and drug product manufacturing facilities are recommended for overall approval based on the firm's inspection history and manufacturing experience. All testing facilities have acceptable compliant status and recommended for approval.

Quality Risk Assessment: Tabulated on the next page.

Quality Risk Assessment: NDA 212593
(Vasopressin Injection)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation**	**Final Risk Evaluation**	**Comments**
Sterility	Formulation Container Closure Process Parameters Scale/Equipment/ Site	**H** **(High)**	(b) (4)	Acceptable	
Endotoxin Pyrogen	Formulation Container Closure Process Parameters Scale/equipment/ Site	**M** **(Moderate)**		Acceptable	Any proposed changes concerning acceptance limits for endotoxin levels may need to be evaluated based on the maximum total daily dose.
Assay (API), Stability	Formulation Container Closure Raw Materials Process Parameters Scale/Equipment/ Site	L (Low)		Acceptable	
Uniformity of Dose – Fill/ deliverable Volume	Formulation Container Closure Process Parameters Scale/equipment/ site	L (Low))		Acceptable	

Final Risk Assessment *(continued)*

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation**	**Final Risk Evaluation**	**Comments**
Osmolality	Formulation Raw materials Process parameters Scale/equipment/ site	L (Low)	(b) (4)	Acceptable	
pH (High)	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)		Acceptable	
Particulate Matter	Formulation Container Closure Process Parameters Scale/equipment/ site	M (Moderate)		Acceptable	
Leachable Extracts	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)		Acceptable	
Appearance	Formulation Raw materials Process Parameters Scale/equipment/ site	L (Low)		Acceptable	

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead (ATL) Assessment and Signature:

From the chemistry, manufacturing, and controls (CMC)/quality perspective, Vasopressin Injection (NDA 212593) is recommended for final approval. A shelf-life of 24 months is approved for the product when stored at long-term storage conditions of 2°C and 8°C (36°F and 46°F) in the proposed commercial container closure system. In addition, product storage is permitted for up to 12 months at controlled room temperature (USP) 20 to 25°C (68 to 77°F) within the expiry date.

Mohan Sapru, M.S., Ph.D.
Application Technical Lead (ATL)
CMC Lead for Division of Cardiology and Nephrology (DCN)
OPQ/ONDP/DNDPIII/NDPB5

Mohan K. Sapru -S

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NDA 212593 (Vasopressin Injection)

Integrated Quality Review

Recommendation: Approval

Drug Name/Dosage Form	Vasopressin Injection
Strength	20 units/mL
Route of Administration	Intravenous Infusion
Rx/OTC Dispensed	Rx
Applicant	American Regent, Inc. (formerly Luitpold Pharmaceuticals, Inc.)
Submissions (s) Reviewed	NDA 212593, and all the submitted CMC amendments

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Monica Cooper	ONDP/DNDPI/NDPBI
Drug Product/Environmental Assessment (EA)	Grace Chiou	ONDP/DNDPI/NDPBI
Process and Facility	Upasana Sahu	OPF/DIA/IABI
Biopharmaceutics	Parnali Chatterjee	ONDP/DB/BBI
Microbiology	Valerie Huse	OPQ/OPF/DMA/MABII
RBPM	Grafton Adams	OPRO DRBPMI/RBPMBI
Application Technical Lead	Mohan Sapru	ONDP/DNDPI/NDPBI

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and controls (CMC)/quality perspective, Vasopressin Injection (NDA 212593) is recommended for approval. Product shelf-life of 24 months is approved for the product when stored at 5°C ± 3°C in the proposed commercial container closure system.

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

Not applicable.

II. Quality Assessment Summary

The applicant, American Regent, Inc. has sought U.S. marketing approval for Vasopressin Injection in accordance with Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act and Section 314.50. Currently, Vasopressin Injection, USP, is an unapproved product marketed in the U.S. by American Regent since 1993. The proposed Vasopressin Injection is indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines. The drug product is to be made available as a 20 USP units/mL sterile solution for intravenous injection. For the approval of this NDA, the applicant relies on the Agency's determination of safety and effectiveness for the Listed Drug (LD) i.e., Vasostrict (NDA 204485), which is manufactured by Par Sterile Products LLC (Par). (b) (4) . Based on the known physicochemical attributes of the LD, USP monograph, and data from multiple laboratory batches, the applicant has adequately defined the quality target product profile (QTPP) for the proposed formulation of Vasopressin Injection. From quality perspective, the proposed control strategies are adequate to ensure consistent product quality with regard to identity, strength, purity, sterility, potency, and stability.

A. Drug Substance (Vasopressin, USP) Quality Summary

Vasopressin is a cyclic peptide, which consists of nine amino acids with a disulfide bridge linking the side chains of two cysteine amino acids. All 9 amino acids are present in their natural L-form, and the C-terminal Gly is present in its amide form. No side-chain or N-terminal modification is present. There are no polymorphic forms known. All CMC information for the drug substance has been referenced to DMF (b) (4), which has been reviewed and found adequate (Review #2, 13-Nov-2019; M. Cooper). Briefly, structural characterization of vasopressin drug substance using appropriate validated analytical procedures is adequate. Specifically, Fourier Transform- Ion Cyclotron Resonance – Mass Spectrometry (FT-ICR MS) technique has been used to confirm the presence of the disulfide bond. As documented in pre-NDA 212593 meeting minutes,

FDA recommended that structural characterization of the drug substance should include the one-time demonstration of sufficient correlation between a bioassay test and the proposed HPLC assay. Based on information provided in the NDA, the applicant has adequately demonstrated that bioactivities determined for 3 vasopressin batches using the bioassay method are well correlated with the content values determined via the HPLC assay. Thus, the HPLC assay is sufficient for batch release testing of the vasopressin drug substance and a routine bioassay test is not needed for release or stability testing. The applicant has used the well-established (b) (4) (b) (4) Specifically, the identity, quality and purity of each batch of the drug substance are assessed and confirmed as per the specification, which includes testing for identification by mass spectrometry and HPLC; amino acid analysis, and determination of vasopressin (assay; (b) (4)) content and peptide-related impurities. Elemental impurities in Vasopressin, USP drug substance have been investigated using screening of elements by inductively coupled plasma atomic emission spectroscopy (ICP-AES) and high resolution inductively coupled plasma atomic mass spectroscopy (HR-ICP-MS). The levels of elemental impurities in the drug substance comply with the Option 1 concentration limits, as specified in ICH Q3D. The bacterial endotoxins and microbial enumeration are controlled as per USP <85> and USP <61>, respectively. The proposed retest period of (b) (4) months for the drug substance is supported by the stability data.

B. Drug Product (Vasopressin Injection) Quality Summary

B.1. Product Design, and Release Specification:

The proposed product, Vasopressin Injection, USP, 20 Units/1 mL in a single-dose 2 mL glass vial, is to be administered by intravenous infusion following dilution with normal saline (0.9% sodium chloride) or 5% dextrose in water. The drug product is formulated in water with chlorobutanol (a preservative) and sodium chloride and acetic acid, (b) (4) There are no novel excipients and no excipients of human or animal origin. It is noted that the use of chlorobutanol as a preservative in a single-dose drug product is atypical and not generally required; however, presence of chlorobutanol in the formulation does not pose any risk to product quality, safety or efficacy. All the product critical quality attributes are controlled by product specification. Specifically, the product release specification includes testing for appearance, identity, assay, degradants, volume of solution, particulate matter, pH, chlorobutanol, (b) (4), endotoxins (USP<85>) and sterility (USP<71>). The level of each excipient used in the manufacture of the drug product is at or below levels typically found in other parenteral products as per the FDA's inactive ingredient database. All the analytical methods have been adequately validated. Based on the risk assessment and testing performed in compliance with ICH Q3D, USP <232>, and USP<233>, no routine release testing of elemental impurities and/or additional controls are required.

B.2. Manufacturing: The manufacturing process is a standard (b) (4) process. The process steps used to manufacture the drug product include: (b) (4) The listed critical material and process parameters are adequate. Based on the control strategy, including in-process controls, and environmental controls, the manufacturing process is adequately controlled.

B.3. Microbiological Aspects: The validated process for (b) (4), and container closure integrity testing performed are adequate. Sterility and bacterial endotoxins tests are performed at release and on stability in accordance with USP <71> and USP <85>, respectively. The product specification meets regulatory expectations for a sterile and preserved drug product.

B.4. Biopharmaceutics Aspects: The proposed drug product has the same active moiety (vasopressin) and is considered to be the same dosage form that involves same route of administration [IV use] and indication as the listed drug (LD), Vasostrict® (vasopressin) for injection, 20 Units/1 mL (NDA 204485). However, the proposed product and the LD are different with regards to the excipients. Specifically, the proposed formulation contains chlorobutanol while the LD does not contain this preservative in the listed dosing configuration. Unlike the LD, the proposed formulation involves the use of sodium chloride (b) (4) In addition, acetic acid is used to adjust the pH of the drug product while the LD uses sodium acetate to adjust the pH. This difference is inconsequential as acetate ions are introduced in both the LD and the proposed formulation. Based on the supporting data from pH and osmolality comparisons, and literature information, differences in the inactive ingredients are not expected to affect the disposition kinetics (the sum of distribution and elimination rates) of vasopressin in the proposed drug product when administered via the IV route. Essentially, the disposition kinetics of vasopressin is expected to be similar after administration of either the proposed product or the LD. The data and information submitted in the application demonstrate that the proposed drug product has been adequately bridged to the LD; therefore, per 21 CFR 320.24(b)(6), an *in vivo* pharmacokinetic study is not needed.

B.5. Container Closure System: Vasopressin Injection, USP 20 units/mL will be packaged in 2-mL (b) (4) type (b) (4) glass vial with a 13 mm stopper, sealed with a (b) (4). The applicant has performed extractable/leachable testing that is compliant with USP <1663> and <1664>. Based on results from glass delamination study, no delamination or formation of glass lamellae in vials has been observed. The stability data indicate that the drug product is compatible with the proposed stoppers and vials. Consistent with the LD, light protection for Vasopressin Injection, USP 20 units/mL is provided via packaging each clear glass vial in an opaque secondary container carton.

B.6. Expiration Date & Storage Conditions: The current stability data, which includes 18 months of long-term and 6 months of accelerated stability data, support a shelf-life of 24 months for the product when stored at 5°C ± 3°C in the proposed commercial container closure system.

C. Assessment of Manufacturing Facilities:

Based on the inspection history, manufacturing experience and acceptable compliant status, the Office of Pharmaceutical Manufacturing Assessment (OPMA) has recommended an overall approval for all the currently listed manufacturing and testing facilities concerning this NDA.

D. Environmental Exclusion:

The applicant's claimed categorical exclusion from the environmental assessment requirements under 21 CFR Part 25.31(a) is acceptable.

E. Any Special Product Quality Labeling Recommendations:

All recommendations have been incorporated by the applicant in the most recent version of the label and labeling.

F. Life Cycle Knowledge Information

On the next page:

Final Risk Assessment: NDA 212593 (Vasopressin Injection)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation**	**Final Risk Evaluation**	**Comments**
Sterility	Formulation Container Closure Process Parameters Scale/Equipment/ Site	**H (High)**	(b) (4)	Acceptable	
Endotoxin Pyrogen	Formulation Container Closure Process Parameters Scale/equipment/ Site	**M (Moderate)**		Acceptable	Any proposed changes concerning acceptance limits for endotoxin levels may need to be evaluated based on the maximum total daily dose.
Assay (API), Stability	Formulation Container Closure Raw Materials Process Parameters Scale/Equipment/ Site	L (Low)		Acceptable	
Uniformity of Dose – Fill/ deliverable Volume	Formulation Container Closure Process Parameters Scale/equipment/ site	L (Low))		Acceptable	

Final Risk Assessment *(continued)*

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation**	**Final Risk Evaluation**	**Comments**
Osmolality	Formulation Raw materials Process parameters Scale/equipment/ site	L (Low)	(b) (4)	Acceptable	
pH (High)	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)		Acceptable	
Particulate Matter	Formulation Container Closure Process Parameters Scale/equipment/ site	M (Moderate)		Acceptable	
Leachable Extracts	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)		Acceptable	
Appearance	Formulation Raw materials Process Parameters Scale/equipment/ site	L (Low)		Acceptable	

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead (ATL) Assessment and Signature:

From the chemistry, manufacturing, and controls (CMC)/quality perspective, Vasopressin Injection (NDA 212593) is recommended for approval. Product shelf-life of 24 months is approved for the product when stored at 5°C ± 3°C in the proposed commercial container closure system.

Mohan Sapru, M.S., Ph.D.
Application Technical Lead (ATL)
CMC Lead for Cardiovascular and Renal Products

Mohan K. Sapru -S

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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: The PI assessed in this review was submitted on 09July 2019. Based on the information provided, there are minor edits to be made to the labeling portion of this submission. Updated container and carton labels are necessary to remove the "preservative free" statement and use of "USP" in the product title. Please see review below. Overall, the product quality aspects of the labeling will be adequate upon the Applicant's acceptance of the proposed revisions.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name Established name(s) Route(s) of administration	Vasopressin injection, USP for intravenous use	Inadequate "USP" needs to be removed; Revise to include a comma before "for intravenous use"
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Injection: 20 units per mL (3)	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.		Inadequate Include "single-dose" container per FDA guidance

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

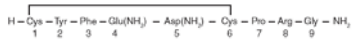
<table>
<tr><th>Item</th><th>Information Provided in the NDA</th><th>Assessor's Comments</th></tr>
<tr><td colspan="3">DOSAGE AND ADMINISTRATION section</td></tr>
<tr><td>Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)</td><td>Dilute vasopressin injection 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
<table><tr><th rowspan="2">Fluid restriction?</th><th rowspan="2">Final concentration</th><th colspan="2">Mix</th></tr><tr><th>Vasopressin Injection</th><th>Diluent</th></tr><tr><td>No</td><td>0.1 units/mL</td><td>2.5 mL (50 units)</td><td>500 mL</td></tr><tr><td>Yes</td><td>1 unit/mL</td><td>5 mL (100 units)</td><td>100 mL</td></tr></table>Inspect parenteral drug products for particulate matter and discoloration prior to use, whenever solution and container permit.</td><td>Adequate</td></tr>
</table>

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s) Strength(s) in metric system If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Vasopressin injection is a clear, [redacted] (b) (4) colorless solution [redacted] (b) (4) available as 20 units/mL in a single dose vial.	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.		Inadequate Include a "–" between "single dose"

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Vasopressin is a polypeptide hormone (b) (4)	Adequate
Dosage form(s) and route(s) of administration		Inadequate Modify to "Vasopressin injection" to be consistent with Highlights
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	Vasopressin injection is a sterile, aqueous solution of synthetic arginine vasopressin for intravenous administration. The 1 mL solution contains vasopressin 20 units/mL, sodium chloride 9 mg, chlorobutanol 0.5%, water for injection, and acetic acid to adjust pH to 3.5.	Remove statement regarding (b) (4). Include statement to clarify dosage, such as: One mg is equivalent to XXX units. Remove "/mL" as this is redundant. Provide the quantity of chlorobutanol present (i.e. 5 mg)
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.		Inadequate Revise to ensure all items are in alphabetical order and include quantity of chlorobutanol
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.		
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA
Statement of being sterile (if applicable)		Adequate
Pharmacological/ therapeutic class	Vasopressin is a polypeptide hormone (b) (4)	Inadequate Revise to include only therapeutic class and remove (b) (4)

Chemical name, structural formula, molecular weight	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	Adequate
If radioactive, statement of important nuclear characteristics.	NA	NA
Other important chemical or physical properties (such as pKa or pH)		Adequate See above: A description of the drug substance powder is provided, and it is stated that the pH is adjusted to 3.5 in the list of excipients (see above).

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	NA	NA
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	No promotional statements.	Adequate

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s) Strength(s) in metric system Available units (e.g., bottles of 100 tablets) Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Vasopressin Injection, USP is a clear, practically colorless solution for intravenous administration available as: NDC 0517-1020-25: A carton of 25 single dose vials each containing vasopressin 1 mL at 20 units/mL.	Inadequate Include a "–" between "single dose"
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	NA	NA
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.		Adequate See above comment.

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Store between 2°C and 8°C (36°F and 46°F). Do not freeze.	Adequate
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant	NA	NA

has a warning such as “Do not eat.”		
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store between 2°C and 8°C (36°F and 46°F). Do not freeze.	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”	NA	NA
Include information about child-resistant packaging	No information included.	Adequate.

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor’s Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	NA	Inadequate Information not included

2.0 PATIENT LABELING

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Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Vasopressin Injection, USP	Adequate
Dosage strength	20 Units per mL	Adequate
Route of administration	For intravenous injection	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance		
Net contents (e.g. tablet count)	1 mL single dose vial	Inadequate
"Rx only" displayed on the principal display	Rx only	Adequate
NDC number	NDA 0517-1020-01	Adequate
Lot number and expiration date	 Black encoding area will contain LOT and EXP	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Store (b) (4) 2°C and 8°C (36°F and 46°F).	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	Single dose vial	Inadequate Include a "–" between "single dose"
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	Must be diluted prior to use.	Adequate
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	NA	NA

Bar code	Present	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	American Reagent, Inc. Shirley, NY 11967	Adequate
Medication Guide (if applicable)	NA	NA
No text on Ferrule and Cap overseal	In 1.14.1 Draft Labeling Intro, the Applicant states, "Please note that in accordance with USP General Chapter <1> Labeling on Ferrules and Cap Overseals, the cap/ferrule overseal is not printed."	Adequate
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	Not stated	Adequate The specifications on stability are aligned with the USP monograph.
And others, if space is available	NA	NA

Assessment of Carton and Container Labeling: Inadequate

The Applicant needs to remove (b) (4) *. Also, "Vasopressin Injection, USP" should be replaced with "Vasopressin Injection." Information Requests will be sent to the Applicant for new carton and container labels.*

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

ITEMS FOR ADDITIONAL ASSESSMENT

Adequate, pending the Applicant's acceptance of the revisions noted above in red.

Overall Assessment and Recommendation:

This application is recommended for approval per labeling/labels perspective once the following changes have been made to the label and carton.

Grace Chiou

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David Claffey

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BIOPHARMACEUTICS

NDA: 212593-ORIG-1
Drug Product Name / Strength: Vasopressin Injection, USP, 20 Units/mL
Route of Administration: Intravenous
Applicant Name: American Regent, Inc.
Primary Reviewer: Parnali Chatterjee, Ph.D.
Secondary Reviewer: Om Anand, Ph.D.

EXECUTIVE SUMMARY:

Background: American Regent, Inc. is seeking approval for Vasopressin Injection, USP, 20 Units/1 mL in a single-dose 2 mL glass vial to be administered by intravenous infusion following dilution to increase blood pressure in adults with vasodilatory shock who remain hypotensive despite catecholamines and fluids. This 505 (b)(2) application relies, for its approval, on FDA's previous findings of safety and effectiveness for the listed drug (LD) Vasostrict® (vasopressin injection) which was approved under NDA 204485 for intravenous use as a single-use vial.

The proposed product is a (b) (4) powder for solution, for intravenous (IV) administration after reconstitution and dilution. The proposed drug product has the same active moiety (vasopressin), and is the same dosage form, for the same route of administration [IV use] and indication as the listed drug (LD), Vasostrict® (vasopressin) for injection, 20 Units/1 mL (NDA 204485).

The proposed product and the reference product are different with regards to the excipients (chlorobutanol and sodium chloride). Based on the supporting data from pH and osmolality comparisons, and literature information, differences in the inactive ingredients are not expected to affect the disposition kinetics of vasopressin in the proposed drug product when administered via the IV route. The disposition kinetics of vasopressin should be similar after administration of these two products.

The data and information submitted in the Application demonstrate that the proposed drug product has been adequately bridged to the LD; therefore, per 21 CFR 320.24(b)(6), an in vivo pharmacokinetic study is not needed.

OVERALL REVIEW RECOMMENDATION:

From the Biopharmaceutics perspective, NDA 212593-ORIG-1 for Vasopressin Injection, USP, [20 Units/mL] is recommended for **APPROVAL.**

BIOPHARMACEUTICS ASSESSMENT

- **LIST OF SUBMISSIONS BEING REVIEWED:**

Submissions Reviewed	Reference ID
Pre-NDA 212593-ORIG-1,	10/09/2018, SDN 2 (\\cdsesub1\evsprod\nda212593\0001\m1\us\12-cover-letters\212593-cover-letter-meeting-package.pdf)
NDA 212593-ORIG-1	03/29/2019, SDN 4 (\\cdsesub1\evsprod\nda212593\0002\m1\us\12-cover-letters\cover-letter-nda-application-29mar2019.pdf)
Information Request Comment 1	07/09/2019, SDN 10 (\\cdsesub1\evsprod\nda212593\0009\m1\us\12-cover-letters\cover-letter-2019-07-09-s0009-filing-communication-response.pdf)
Information Request Comment 2	10/11/2019, SDN 14 (\\cdsesub1\evsprod\nda212593\0013\m1\us\12-cover-letters\cover-letter-2019-10-11-s0013-ir.pdf)

- ***DRUG SUBSTANCE*:**

The active ingredient in the proposed drug product is vasopressin ($C_{46}H_{65}N_{15}O_{12}S_2$, free base, molecular weight 1083.4 Da) or arginine vasopressin (AVP), an endogenous neuroendocrine hormone with nine (9) aminoacids and a disulfide bond. The peptide is (b) (4) and is hygroscopic. The hormone is produced in the hypothalamus and released from the posterior pituitary. The primary function of AVP is to regulate plasma osmolality and extracellular fluid volume.

- ***Solubility:*** According to the Applicant, the proposed drug substance exhibits high solubility in buffer solutions across the physiological pH 1.2-13 (see **Table 1**).

Table 1. Solubility of Vasopressin, USP in buffer solutions across the physiological pH

Low pH	1% Acetic Acid	Freely soluble
Neutral pH	Water	Very soluble
High pH	0.1M NaOH	Freely soluble

- ***Permeability:*** The drug substance has two pKa's: pKa1=15.7 and pKa2=-1.8. The pH of a 5 mg/mL solution in water is 5.2. The isoelectric point (pI) of the peptide is 11.3. The current submission does not include any in vitro permeability data. Based on the pharmacokinetic data provided in the Prescribing Information (PI) for the listed drug (LD), Vasostrict® (vasopressin

injection) which was approved under NDA 204485, approximately 6% of the administered dose is excreted unchanged in the urine. Vasopression is extensively metabolized in the liver. The apparent half-life ($t_{1/2}$) of vasopressin is $\leq$ 10 minutes at infusion rates of 0.01-0.1 units/minute, with a high clearance of 9 to 25 mL/min/Kg in patients with vasodilatory shock.

- ***DRUG PRODUCT*:**

The proposed drug product is a sterile, single-use 2 mL vial containing 20 Units of vasopressin drug substance, 5 mg chlorobutanol, NF, normal saline (0.9% w/v sodium chloride in water for injection) in 1 mL volume. The pH of the drug product is adjusted to 3.5 with acetic acid, USP. The drug product is a clear, sterile solution ready for infusion following dilution.

According to the Applicant, the proposed drug product is qualitatively (Q1) and quantitatively (Q2) similar with the Listed Drug (LD), Vasostrict® (vasopressin injection) that was approved in 2014. The qualitative and quantitative composition of the proposed drug product and the LD is shown in **Table 2**. The proposed drug product contains vasopressin, the drug substance which is present in the LD. However, it should be noted that the proposed drug product also contains two additional components, 0.9% w/v sodium chloride and chlorobutanol, which is not included in the single-use 1 mL LD. Chlorobutanol acts as a preservative and is included in the 1 mL multi-dose vial of the LD.

Table 2. Qualitative (Q1) and quantitative (Q2) composition of the proposed drug product and the LD, Vasostrict® (vasopressin injection)

Component	American Regent's Historical and Current Formulation		Par's Formulation Prior to 2016		Par's Current Formulation	
	mg/mL	% wt/wt	mg/mL	% wt/wt	mg/mL	% wt/wt
Vasopressin, USP	20 units/mL	0.004% wt	20 units/mL	0.004% wt	20 units/mL	0.004% wt
Chlorobutanol, NF	5 mg/mL	0.5% wt	5 mg/mL	0.5% wt	N/A	
Acetic Acid, USP	pH Adjust		pH Adjust		N/A	
Sodium Chloride, USP	9 mg/mL	0.9% wt	N/A		N/A	
Sodium Acetate, USP	N/A		N/A		NS	
pH	3.5		3.4 – 3.6		3.8	
Water for Injection, USP	Q.S.		Q.S.		Q.S.	
[redacted] (b) (4)						

N/A = Not Applicable NS = Not Specified

The original formulation for the LD, Vasostrict® (vasopressin injection), 20 Units/mL included 0.5% w/w chlorobutanol as a preservative in 1 mL multi-dose vial. However, the current formulation for the LD does not contain chlorobutanol (see Table 2).

According to the Applicant, 0.9% w/v sodium chloride in the proposed drug product functions as [redacted] (b) (4). Due to the inclusion of 0.9% w/v sodium chloride, the osmolality of the undiluted proposed drug product is significantly higher (see **Table 3**). As the proposed product is for intravenous administration; the drug product will be diluted to 0.1 units/mL or 1 unit/mL with either 0.9% normal saline or 5% dextrose for injection to either 500 mL or 100 mL prior to

administration, hence the inclusion of added 0.9% w/v sodium chloride will likely have minimal effect on the pharmacokinetics of the drug product.

Because of the differences in the osmolality between the undiluted and diluted proposed drug product, the Applicant was recommended to include osmolality as a drug product specification in an *Information Request*. Additionally, the Applicant was recommended to provide osmolality for three registration batches of the undiluted and diluted drug product.

Table 3. Osmolality of the proposed Vasopressin Injection, USP, 20 Units/1 mL drug product and the LD, Vasostrict® (vasopressin injection, USP)

Parameter	Vasostrict®			Lab Batch (b) (4) 170630-2
	Lot 821057 (Exp. 09/2018)	Lot 301435 (Exp. 02/2019)	Lot 304395 (Exp. 05/2019)	
pH	3.89	3.89	3.87	3.50
Density (g/mL)	0.9978	0.9975	0.9975	1.0058
Osmolality (mOsm/kg)[1]	25, 25	24, 23	24, 22	323, 323

Effect of pH on the solubility of vasopressin:
During the development of the proposed drug product, the Applicant evaluated the effect of pH change on the solubility of vasopressin and chlorobutanol in the drug product. The Applicant manufactured two batches, 8 (b) (4) 180104-1 at pH 2.5 and 8 (b) (4) 180104-1 at pH 4.5 and placed them under long-term stability (5°C) for six (6) months in inverted position. The solubility of vasopressin and chlorobutanol were evaluated at up to 6 months (see **Table 4**). From the solubility data provided in **Table 4**, pH 2.5 and 4.5 has minimal effect on the solubility of vassopression and chlorobutanl over 6 months under long-term stability (5°C).

Table 4. Effect of pH on the solubility of vasopressin and chlorobutanol in the proposed Vasopressin Injection, USP, 20 Units/1 mL drug product

Sample (8 (b) (4) 180104-1[a]) (8 180104-2[b])	Storage at Long Term Storage Conditions (5°C)			
	Sample pH	Vasopressin Assay (%LC)	Chlorobutanol Assay (%LC)	pH
Control	pH 2.5	100.9	96.7	2.52
	pH 4.5	100.0	95.8	4.48
3 Months	pH 2.5	96.6	96.9	2.54
	pH 4.5	97.8	94.5	4.48
6 Months	pH 2.5	96.3	96.9	2.57
	pH 4.5	100.3	95.4	4.48

[a] Lab Batch produced on 01/04/18, Notebook (b) (4) 8 pages 4-5
[b] Lab Batch produced on 01/04/18, Notebook 8 pages 4-5

Presence of chlorobutanol as a preservative in the proposed drug product:
This Reveiwer also conductd a review of the literature on chlorobutanol in PubMed and found no evidence showing that chlorobutanol can potentially affect the disposition kinetics of vasopressin in the proposed drug product when administered via the IV route.

In addition, this Reviewer notes that the FDA first approved Vasostrict®, 20 Units/mL on April 17, 2014. The formulation approved in the original NDA contained vasopressin, acetic acid, chlorobutanol, and water for injection in a 1 mL vial presentation. In March 2016, FDA approved supplemental application S-003, which proposed a formulation change to Vasostrict®, Units/mL . This new formulation for the 20 Units/mL presentation contains vasopressin, water for injection, and sodium acetate for pH adjustment and does not contain chlorobutanol. The FDA previously determined that the original Vasostrict®, Units/mL, formulation was not discontinued from sale for reasons of safety or effectiveness[1].

- ***WAIVER REQUEST FOR THE PROPOSED DRUG PRODUCT:***

Based on qualitatively (Q1) and quantitatively (Q2) similarity between the proposed product with the Listed Drug (LD), Vasostrict® (vasopressin injection) that was approved prior to 2016 (**Table 2)**, the Applicant requested a waiver of in vivo bioequivalence (BE) studies for the proposed drug product as per 21 CFR§320.22 (a). The request for waiver was based on 21 CFR§320.22 (b) as the drug product is a parenteral solution for intravenous administration and has the same active ingredient, vasopressin, at the same concentration as the LD, therefore the in vivo BA/BE would be self-evident. Because, the proposed drug product contains chlorobutanol which is not in the 1mL LD, but in the 10 mL LD, the biowaiver request cannot be granted based on the qualitative and quantitative sameness as per 21 CFR§320.22 (a).

However, the Applicant provided comparative physico-chemical characterization to highlight the similarities between the proposed drug product and the LD.

Table 5. Physicochemical characterization of proposed Vasopressin Injection, USP, 20 Units/1 mL drug product and the LD

Lot	pH	Vasopressin %L.C.	Chlorobutanol %L.C.	Total Impurities (%)	Single Largest Unknown Impurity (%)	Appearance
Vasopressin Injection, USP Exhibit Batch X16200	3.63 3.62	100.3% 100.8%	97.6% 101.8%	(b) (4)		A clear, practically colorless solution
Vasopressin Injection, USP Exhibit Batch X16300	3.64 3.64	98.9% 99.3%	100.6%, 101.6%			A clear, practically colorless solution
Vasopressin Injection, USP Exhibit Batch X16400	3.62 3.62	100.6% 100.3%	101.8%, 102.4%			A clear, practically colorless solution
Vasostrict® Lot 821057 (Exp: 9/2018)	3.89	101.6	N/A			A clear, practically colorless solution
Vasostrict® Lot 301435 (Exp: 2/2019)	3.89	102.1	N/A			A clear, practically colorless solution
Vasostrict® Lot 304395 (Exp: 5/2019)	NT	99.9	N/A			A clear, practically colorless solution

N/A = Not Applicable NT = Not Tested

[1] Docket No. FDA-2017-P-1096: https://www.regulations.gov/document?D=FDA-2017-P-1096-0004

Vasostrict®	ARI's Proposed Product Vasopressin Injection, USP	Justification
Dilute to 0.1 Units/mL or 1 Units/mL with normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W).	Dilute to 0.1 Units/mL or 1 Units/mL with normal saline (0.9% sodium chloride) or 5% dextrose in water (D5W).	Identical. Dilution scheme is provided in Vasostrict® package insert.
Administered as an IV infusion	Administered as an IV infusion	Identical. Route of administration is provided in Vasostrict® package insert.
Appearance 1 Unit/mL and 0.1 Unit/mL in 0.9% NaCl: Not available 1 Unit/mL and 0.1 Unit/mL in 5% Dextrose: A clear, practically colorless solution	**Appearance** 1 Unit/mL and 0.1 Unit/mL in 0.9% NaCl and 1 Unit/mL and 0.1 Unit/mL in 5% Dextrose: A clear, practically colorless solution	Identical. Composition, strength, storage durations and storage conditions align with those specified in Vasostrict® package insert.
After dilution to 1 unit/mL in 0.9% NaCl: 275 mOsm/kg 274 mOsm/kg	After dilution to 1 unit/mL in 0.9% NaCl: 286 mOsm/kg 285 mOsm/kg	The osmolality of 0.9% NaCl was determined to be 285 mOsm/kg and 284 mOsm/kg. At the dilutions specified on the label, the diluent serves as the primary contributor to the osmolality even at 1 unit/mL. At 0.1 units/mL, the contribution of the diluent to the final osmolality will be even greater. As such, differences in the final osmolality of both the Luitpold product and the Vasostrict® product will be negligible at the time of administration.

In order to confirm that the osmolality of the proposed drug product concentrate and the diluted product for infusion would be similar to those of the LD, an Information Request was conveyed to the Applicant on 09/25/2019 to provide osmolality data for three registration batches of the drug product, LD concentrate, and the diluted product for infusion. The Applicant responded to the *Information Request* on 10/11/2019 (SDN 14) and provided the requested information for the proposed product (refer to **Table 6a, Table 6b,** and **Table 6c**) and for the LD (see **Table 6d**).

Table 6a. pH and osmolality of the undiluted samples of the proposed Vasopressin Injection, USP, 20 Units/1 mL drug product

Undiluted Drug Product						
Lot	**pH**			**Osmolality (mOsm/kg)**		
X16200	3.65	3.63	3.65	332	332	333
X16300	3.65	3.66	3.65	324	329	332
X16400	3.62	3.62	3.62	330	329	330

Table 6b. pH and osmolality of the diluted samples (to 0.1 Units/mL) of the proposed Vasopressin Injection, USP, 20 Units/1 mL drug product

After Dilution to 0.1 units/mL Vasopressin														
Diluent	**Lot**	**Hold Conditions**	**pH at T_0**			**Osmolality at T_0 (mOsm/kg)**			**pH at T_{hold}**			**Osmolality at T_{hold} (mOsm/kg)**		
0.9% NaCl	X16200	18 hrs at 20-25°C	5.29	5.23	5.27	292	294	305	5.31	5.34	5.26	293	292	294
		24 hrs at 2-8°C	5.03	5.25	5.37	286	292	291	5.23	5.36	5.29	297	290	293
	X16300	18 hrs at 20-25°C	5.24	5.34	5.38	292	294	301	5.53	5.38	5.37	300	295	294
		24 hrs at 2-8°C	5.35	5.37	5.25	291	291	292	5.36	5.24	5.3	290	296	292
	X16400	18 hrs at 20-25°C	5.26	5.26	5.25	294	304	293	5.05	5.41	5.38	294	293	293
		24 hrs at 2-8°C	5.35	5.43	5.29	289	290	289	5.26	5.31	5.33	291	292	293
5% Dextrose	X16200	18 hrs at 20-25°C	4.64	4.60	4.70	273	273	274	4.65	4.66	4.73	273	272	281
		24 hrs at 2-8°C	4.73	4.77	4.73	275	271	282	4.71	4.67	4.62	271	273	272
	X16300	18 hrs at 20-25°C	4.67	4.66	4.70	272	273	275	4.68	4.67	4.68	273	275	272
		24 hrs at 2-8°C	4.71	4.69	4.70	272	274	274	4.72	4.66	4.65	274	271	271
	X16400	18 hrs at 20-25°C	4.68	4.64	4.63	279	274	275	4.66	4.63	4.67	273	274	274
		24 hrs at 2-8°C	4.71	4.77	4.68	272	270	274	4.67	4.68	4.62	272	274	276

Table 6c. pH and osmolality of the diluted samples (to 1 Units/mL) of the proposed Vasopressin Injection, USP, 20 Units/1 mL drug product

After Dilution to 1 unit/mL Vasopressin														
Diluent	**Lot**	**Hold Conditions**	**pH at T_0**			**Osmolality at T_0 (mOsm/kg)**			**pH at T_{hold}**			**Osmolality at T_{hold} (mOsm/kg)**		
0.9% NaCl	X16200	18 hrs at 20-25°C	4.35	4.34	4.35	292	292	294	4.34	4.35	4.36	291	299	293
		24 hrs at 2-8°C	4.37	4.37	4.36	289	292	293	4.34	4.3	4.31	294	294	291
	X16300	18 hrs at 20-25°C	4.34	4.36	4.37	294	294	293	4.38	4.38	4.37	302	295	299
		24 hrs at 2-8°C	4.41	4.38	4.40	292	293	294	4.32	4.32	4.31	292	291	290
	X16400	18 hrs at 20-25°C	4.35	4.33	4.34	294	293	291	4.34	4.34	4.34	300	294	295
		24 hrs at 2-8°C	4.36	4.34	4.34	292	292	292	4.27	4.27	4.27	293	294	302
5% Dextrose	X16200	18 hrs at 20-25°C	4.28	4.27	4.24	277	279	276	4.25	4.25	4.24	278	281	277
		24 hrs at 2-8°C	4.26	4.31	4.27	274	274	272	4.25	4.21	4.21	276	276	280
	X16300	18 hrs at 20-25°C	4.28	4.27	4.26	275	276	277	4.27	4.27	4.26	276	277	275
		24 hrs at 2-8°C	4.29	4.29	4.29	265	272	274	4.23	4.19	4.20	274	274	275
	X16400	18 hrs at 20-25°C	4.27	4.28	4.26	279	275	279	4.27	4.27	4.26	277	277	276
		24 hrs at 2-8°C	4.35	4.34	4.35	278	273	274	4.34	4.35	4.36	275	274	277

Based on the pH and osmolality data provided for the diluted samples (to 0.1 Units/mL and 1 Units/mL) of the proposed product in **Table 6b** and **Table 6c**, it can be seen that the osmolality of the diluted samples for three batches of the proposed drug product is between 265-305 mOsmol/Kg and similar to that of the LD (see **Table 6d**, 274-275 mOsmol/Kg).

Table 6d. pH and osmolality of the undiluted and diluted samples of the Listed Drug (LD), Vasostrict® (vasopressin injection)

Listed Drug – Vasostrict® (Lot 304395)		
Parameter	**Undiluted Drug Product**	**After Dilution to 1 unit/mL in 0.9% Sodium Chloride**
pH	3.87	Not Available
Osmolality	22 mOsm/kg 24 mOsm/kg	275 mOsm/kg 274 mOsm/kg

REVIEWER'S ASSESSMENT : **Adequate**

The data from pH and osmolality comparisons indicate that the differences in the inactive ingredients are not expected to affect the pH and osmolality when the proposed drug product is diluted to 0.1 and 1 Units/mL and administered *via* the IV route. The minor difference between the formulations with regard to preservatives and buffers are not likely to affect the distribution/disposition kinetics/ PK profile of vasopressin *via* the IV route.

Per 21 CFR 320.24(b)(6), FDA can rely on any other approach deemed adequate to establish the bridge (bioavailability/bioequivalence) between the listed and proposed drug products. Therefore, based on the totality of the information provided, the Applicant has established an appropriate bridge between the proposed drug product and the LD.

Parnali Chatterjee

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Om Anand

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	212593
Assessment Cycle Number	01
Drug Product Name/ Strength	Vasopressin Injection, USP, 20 units/mL
Route of Administration	Intravenous
Applicant Name	American Regent, Inc.
Therapeutic Classification/ OND Division	
Manufacturing Site	American Regent, Inc. 4150 Lyman Drive Hilliard, Ohio 43026 FEI: 3005761472
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
212593 Orig-1	29 March 2019
/Quality/Response to Information Request	01 July 2019
Multiple Categories/Subcategories (Labeling)	09 July 2019
TRIAGE-1 (Quality/Response to Information Request)	26 August 2019
/Quality/Response to Information Request	11 October 2019

Highlight Key Issues from Last Cycle and Their Resolution: Not applicable.

Remarks: The RLD is NDA 204485. This drug product is indicated for the increase of blood pressure in adults with vasodilatory shock who remain hypotensive despite fluids and catecholamines.

Concise Description of Outstanding Issues

-

Supporting Documents:

- DMF (b) (4) (Type V), (b) (4) . The relevant information was reviewed in "D (b) (4) M33R01.doc", dated 03 February 2017 and deemed "Adequate".

S DRUG SUBSTANCE

The drug substance is not provided sterile. Therefore, a product quality microbiology review of the drug substance is not performed.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

(3.2.P.1 description-and-composition)
(3.2.P.5.1 specifications)
(1.14.1.3 draft-labeling-text)

- **Description of drug product –** The drug product solution is a sterile and preserved, clear and "practically colorless" solution packaged as a single-dose 2 mL vial (1 mL fill) with 13-mm stopper.

- **Drug product composition –**

Ingredient	Quantity per mL	Function
Vasopressin, USP	20 units	API
Chlorobutanol, NF	5 mg	Preservative
Acetic Acid, USP	pH adjust	pH Adjusting Agent
Sodium Chloride, USP	9 mg	(b) (4)
Water for Injection, USP	Q.S.	Solvent
(b) (4)		

- **Description of container closure system –**

Component	American Regent Code #	Description	Manufacturer
Vial	RH1038	2 mL, (b) (4) glass, Type (b) (4) 13-mm (b) (4) (b) (4	(b) (4)
Stopper	RK1002		
Cap	RL1113		

Assessment: ***Adequate***
The description of the drug product, composition and container/closure system meet regulatory expectations.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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Marla Stevens Riley

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