

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

204640Orig1s012

Trade Name: ADRENALIN

Generic or Proper Name: epinephrine injection

Sponsor: Par Sterile Products LLC

Approval Date: August 17, 2021

Indication: Adrenalin® is a non-selective alpha and beta adrenergic agonist indicated for:

- Emergency treatment of allergic reactions (Type 1), including anaphylaxis
- To increase mean arterial blood pressure in adult patients with hypotension associated with septic shock

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204640Orig1s012

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APPLICATION NUMBER:

204640Orig1s012

APPROVAL LETTER



NDA 204640/S-012

APPROVAL LETTER

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

Dear Ms. Nowalski:

Please refer to your Supplemental New Drug Application (sNDA) dated and received September 13, 2019, and your amendments, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Adrenalin (epinephrine injection, USP) 1 mg/mL.

We acknowledge receipt of your amendment dated April 29, 2021, which constituted a complete response to our January 9, 2020, action letter.

This Prior Approval supplemental new drug application provides for a reduction in the

(b) (4)

APPROVAL

We have completed our review of this supplemental application, as amended. This supplement is approved.

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 Teicher Agosto, Regulatory Business Process Manager, at (240) 402 - 3777.

Sincerely,

{See appended electronic signature page}

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



Ramesh
Raghavachari

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204640Orig1s012

OTHER ACTION LETTERS



NDA 204640/S-012

COMPLETE RESPONSE

Par Sterile Products LLC
Attention: Carla English
Associate Director, Regulatory Affairs
Six Ram Ridge Road
Chestnut Ridge, NY 10977

Dear Ms. English:

Please refer to your Supplemental New Drug Application (sNDA) dated and received September 13, 2019, and your amendment, pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Adrenalin (epinephrine injection, USP) 1 mg/mL.

This Prior Approval supplemental new drug application proposes for a reduction in the

(b) (4)

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

1. Based on the reasons for which the (b) (4) was granted, the justification for the removal of (b) (4) is inadequate. Provide adequate justification with data.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the supplemental application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft FDA Guidance for Industry, "Formal Meetings Between the FDA and Sponsors or

NDA 204640/S-012

Page 2

Applicants of PDUFA Products,” December 2017 at <https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM590547>.

If you have any questions, call Phillip Williams, Regulatory Business Process Manager, at (240) 402 - 3974.

Sincerely,

{See appended electronic signature page}

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



Ramesh
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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204640Orig1s012

PRODUCT QUALITY REVIEW(S)

**Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls**

1. **NDA Supplement Number: NDA-204640-SUPPL-12-AMEND-135**

2. **Submission(s) Being Reviewed:**

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement	PA	09/13/2019	09/13/2019	09/18/2019	01/13/2020	12/16/2019
Amendmen-119	PA	11/18/2019	11/18/2019	11/18/2019	01/13/2020	12/17/2019
Amendment-135*	PA	04-29-2021	04-29-2021	05-10-2021	08-29-2021	08-13-2021
IR Response*	PA	08-09-2021	08-09-2021	08-10-2021	08-29-2021	08-10-2021

* **Subjects of current review**

3. **Provides For:**

Removal of (b) (4)

4. **Review #:** 1

5. **Clinical Review Division:** Division of Pulmonary, Allergy and Critical Care (DPACC)

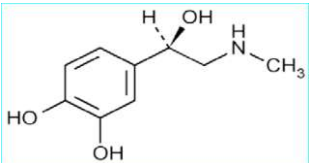
6. **Name and Address of Applicant:**

Katharine Nowalski, Sr. Manager
Par Sterile Products, LLC
Six Ram Ridge Road
Chestnut Ridge, NY, 10977
Tel 248-656-5282
Fax 845-573-5795
nowalski.katharine@endo.com

7. **Drug Product:**

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
Adrenalin (epinephrine injection)	Injection	30 mg/30 mL (1 mg/mL)	Intramuscular, Subcutaneous and Intravenous	Rx	No

8. **Chemical Name and Structure of Drug Substance:**

	<p>USAN: Epinephrine Chemical name: 1,2-Benzenediol, 4-[(1R)-1-hydroxy-2-(methylamino)ethyl]-, or (-)-3,4-Dihydroxy-α-[2-(methylamino)ethyl]benzyl alcohol Molecular formula: C₉H₁₃NO₃ MW: 183.2</p>
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9. Indication:

Emergency treatment of allergic reactions (Type 1), including anaphylaxis.

10. Supporting/Relating Documents: *SDN 135. SDN 137*

11. Consults: *None*

12. Executive Summary:

The supplement 012 to NDA 204-640 provides for elimination of (b) (4) of Epinephrine.

The stability data for Adrenalin® 30 mL drug product batches manufactured without (b) (4) are provided through the 18-month interval at long-term (25°C/60% RH) and 6 months accelerated conditions (40°C/75% RH) at both inverted and upright orientations.

The real time 18-month long-term stability data supports the proposed 18-month finished product expiry for Adrenalin® 30 mL manufactured without (b) (4).

13. Conclusions & Recommendations:

This PA supplement is recommended for approval.

14. Comments/Deficiencies to be Conveyed to Applicant: *None*

15. Primary Reviewer:

Chong Ho Kim, Ph.D.
CMC Reviewer
Branch 1, Division of Post-Marketing Activities I
Office of Lifecycle Drug Products
Office of Pharmaceutical Quality (OPQ)

16. Secondary Reviewer:

Ramesh Raghavachari, Ph.D.
Branch Chief
Branch 1, Division of Post-Marketing Activities I
Office of Lifecycle Drug Products
Office of Pharmaceutical Quality (OPQ)

CMC Assessment

I. Background Information

This amendment-135 is the Applicant's Response to the Agency's Complete Response Letter dated January 9, 2020.

It is stated that Par is providing real time stability data through 18 months, accelerated stability data through 6 months, the revised drug product specification, and executed batch record.

Par manufactured (b) (4) Adrenalin® 30 mL exhibit batches without (b) (4) and placed the batches on long-term and accelerated stability. Real time stability data for these batches is available through 18 months, as well as accelerated stability data through 6 months. The data supports the proposed 18-month finished product expiry for Adrenalin® 30 mL manufactured without (b) (4). A summary of this data is provided in Section 3.2.P.8.1 and the data tables are provided in Section 3.2.P.8.3.

The drug product specification was updated to tighten the (b) (4) shelf-life limits to (b) (4)%. The proposed changes to the current commercial drug product specification is provided in Table 1.

Table 1: Drug Product Specifications

Test/Procedure	Acceptance Criteria	
	Current Commercial Specification	Proposed Specification (b) (4)
(b) (4)		

The exhibit batch records for the aforementioned (b) (4) exhibit batches are provided in Section 3.2.R.1.P.1.

II. Proposed Changes

Removal of the (b) (4).

III. Data Submitted to Support the Proposed Changes:

3.2.P.5 Control of Drug Product

3.2.P.5.1 Specification(s)

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(b) (4)

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

The stability data for Adrenalin® 30 mL drug product batches manufactured without (b) (4) are provided through the 18-month interval at long-term (25°C/60% RH) and 6 months accelerated conditions (40°C/75% RH) at both inverted and upright orientations in Section 3.2.P.8.3.

A summary of this stability data is provided in this section. The 18-month long-term stability data supports the proposed 18-month finished product expiry for Adrenalin® 30 mL manufactured without (b) (4).

(b) (4)

Adrenalin 30 mL (b) (4) Stock # IN500573

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(b) (4)

In summary, 18 months real time stability data look good. All stability parameters meet and exceed an 18-month shelf life at controlled room temperature.

CONCLUSION AND RECOMMENDATION

The stability data for Adrenalin® 30 mL drug product batches manufactured without (b) (4) are provided through the 18-month interval at long-term (25°C/60% RH) and 6 months accelerated conditions (40°C/75% RH) at both inverted and upright orientations.

The real time 18-month long-term stability data supports the proposed 18-month finished product expiry for Adrenalin® 30 mL manufactured without (b) (4).

IV. Risk Associated with the Proposed Changes and Impact to Product Quality and Patient Safety

Low



Chong Ho
Kim

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Raghavachari

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**Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls**

1. **NDA Supplement Number: NDA-204640-SUPPL-12-AMEND-135**

2. **Submission(s) Being Reviewed:**

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
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IR Response*	PA	08-09-2021	08-09-2021	08-10-2021	08-29-2021	08-10-2021

* **Subjects of current review**

3. **Provides For:**

Removal of (b) (4)

4. **Review #:** 1

5. **Clinical Review Division:** Division of Pulmonary, Allergy and Critical Care (DPACC)

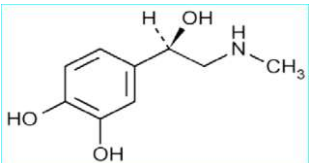
6. **Name and Address of Applicant:**

Katharine Nowalski, Sr. Manager
Par Sterile Products, LLC
Six Ram Ridge Road
Chestnut Ridge, NY, 10977
Tel 248-656-5282
Fax 845-573-5795
nowalski.katharine@endo.com

7. **Drug Product:**

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
Adrenalin (epinephrine injection)	Injection	30 mg/30 mL (1 mg/mL)	Intramuscular, Subcutaneous and Intravenous	Rx	No

8. **Chemical Name and Structure of Drug Substance:**

	<p>USAN: Epinephrine Chemical name: 1,2-Benzenediol, 4-[(1R)-1-hydroxy-2-(methylamino)ethyl]-, or (-)-3,4-Dihydroxy-α-[2-(methylamino)ethyl]benzyl alcohol Molecular formula: C₉H₁₃NO₃ MW: 183.2</p>
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9. Indication:

Emergency treatment of allergic reactions (Type 1), including anaphylaxis.

10. Supporting/Relating Documents: *SDN 135. SDN 137*

11. Consults: *None*

12. Executive Summary:

The supplement 012 to NDA 204-640 provides for elimination of (b) (4) of Epinephrine.

The stability data for Adrenalin® 30 mL drug product batches manufactured without (b) (4) are provided through the 18-month interval at long-term (25°C/60% RH) and 6 months accelerated conditions (40°C/75% RH) at both inverted and upright orientations.

The real time 18-month long-term stability data supports the proposed 18-month finished product expiry for Adrenalin® 30 mL manufactured without (b) (4)

13. Conclusions & Recommendations:

This PA supplement is recommended for approval.

14. Comments/Deficiencies to be Conveyed to Applicant: *None*

15. Primary Reviewer:

Chong Ho Kim, Ph.D.
CMC Reviewer
Branch 1, Division of Post-Marketing Activities I
Office of Lifecycle Drug Products
Office of Pharmaceutical Quality (OPQ)

16. Secondary Reviewer:

Ramesh Raghavachari, Ph.D.
Branch Chief
Branch 1, Division of Post-Marketing Activities I
Office of Lifecycle Drug Products
Office of Pharmaceutical Quality (OPQ)

CMC Assessment

I. Background Information

This amendment-135 is the Applicant's Response to the Agency's Complete Response Letter dated January 9, 2020.

It is stated that Par is providing real time stability data through 18 months, accelerated stability data through 6 months, the revised drug product specification, and executed batch record.

Par manufactured (b)(4) Adrenalin® 30 mL exhibit batches without a (b)(4) and placed the batches on long-term and accelerated stability. Real time stability data for these batches is available through 18 months, as well as accelerated stability data through 6 months. The data supports the proposed 18-month finished product expiry for Adrenalin® 30 mL manufactured without (b)(4). A summary of this data is provided in Section 3.2.P.8.1 and the data tables are provided in Section 3.2.P.8.3.

The drug product specification was updated to tighten the (b)(4) shelf-life limits to (b)(4)%. The proposed changes to the current commercial drug product specification is provided in Table 1.

Table 1: Drug Product Specifications

Test/Procedure	Acceptance Criteria	
	Current Commercial Specification	Proposed Specification (b)(4)
		(b)(4)

The exhibit batch records for the aforementioned (b)(4) exhibit batches are provided in Section 3.2.R.1.P.1.

II. Proposed Changes

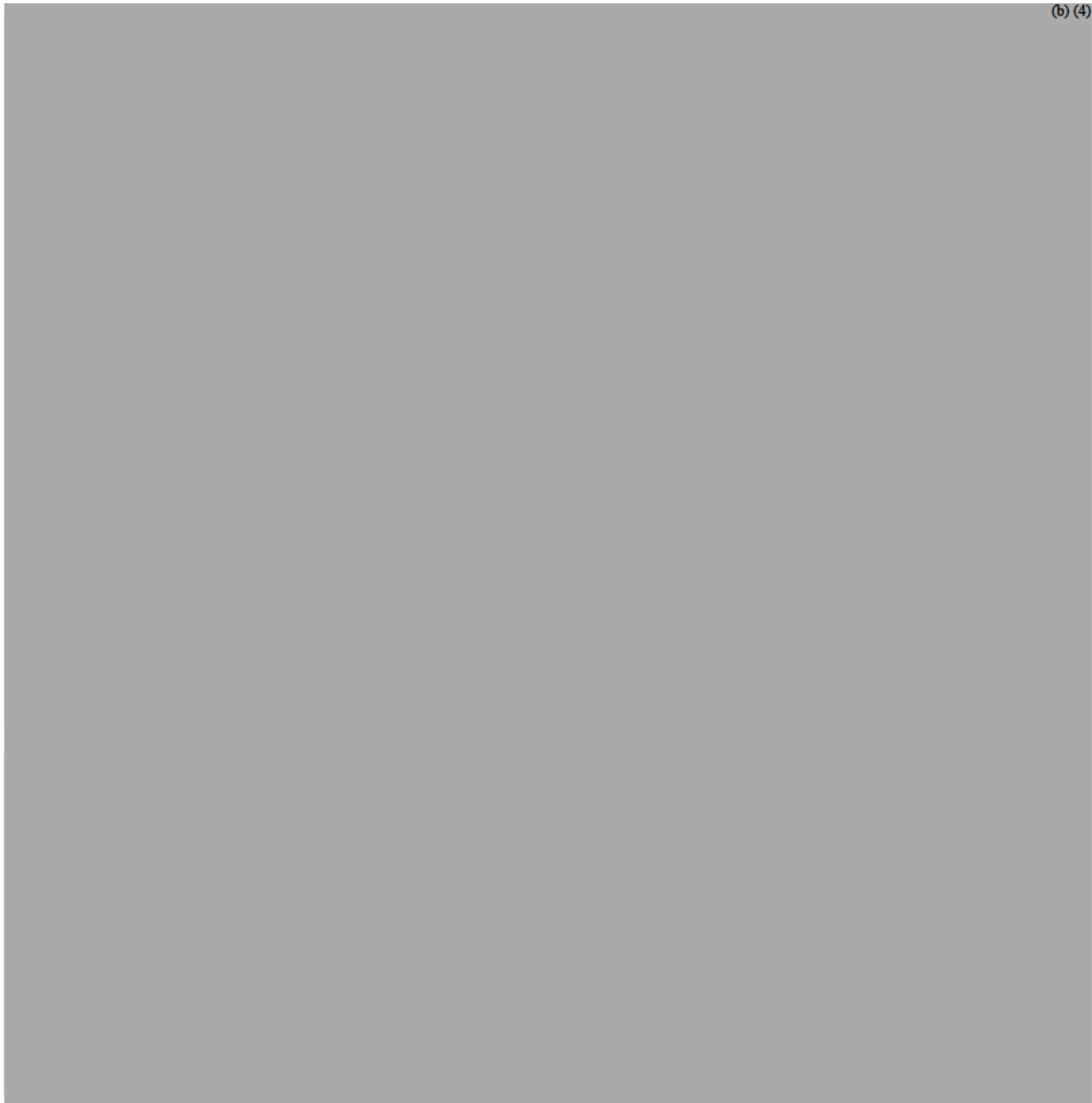
Removal of (b)(4).

III. Data Submitted to Support the Proposed Changes:

3.2.P.5 Control of Drug Product

3.2.P.5.1 Specification(s)

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3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion

The stability data for Adrenalin® 30 mL drug product batches manufactured without (b) (4) are provided through the 18-month interval at long-term (25°C/60% RH) and 6 months accelerated conditions (40°C/75% RH) at both inverted and upright orientations in Section 3.2.P.8.3.

A summary of this stability data is provided in this section. The 18-month long-term stability data supports the proposed 18-month finished product expiry for Adrenalin® 30 mL manufactured without (b) (4).



Adrenalin 30 mL (b) (4) Stock # IN500573

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(b) (4)

DISCUSSION AND CONCLUSIONS

Changes observed on stability were consistent with the chemistry of epinephrine and bisulfite and consistent with trends observed in current commercial Adrenalin 30 mL drug product.

No orientation dependence is observed for any tests.

(b) (4)

All remaining attributes meet and exceed an 18-month shelf life at controlled room temperature.

3.2.P.8.3 Stability Data

Stability data for Adrenalin® 30 mL batches, manufactured without (b) (4), are provided in this section.

Pull dates, for each time point, are reflected on the actual stability data tables. The pull dates provided on the data tables are the actual dates the samples were pulled out of the chamber.

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Chong Ho
Kim

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Raghavachari

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/s/

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