BIOSPECTRA
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L-ARGININE HYDROCHLORIDE 2024 LONG-TERM STABILITY REPORT

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1. OVERVIEW:

The purpose of this report is to analyze and conclude on the data obtained from the long-term stability study of the L-Arginine Hydrochloride. Testing intervals are designated by T_n, where n = the number of months on stability. Testing is performed every three months for the first year, every six months for the second year and annually for each subsequent year in order to maintain that the product remains stable under the specified conditions and for the specified interval of time. The analysis of the compiled data may also aid in a re-evaluation of the retest date for the product.

This long-term stability report assesses the stability of three lots of L-Arginine Hydrochloride; S/2309001, S/2309002 and S/2309003 that completed twelve (12) months of long-term stability in February 2025. The study includes the analyses listed in Table 1 below. Results from all analyses are summarized in Tables 4 through 6.

TABLE 1: STABILITY SPECIFICATIONS

Analysis	Specification
Appearance	White or almost white crystalline powder or colorless crystals
Assay (Dried Basis) (USP/EP/JP)	98.5 – 101.0%
Chloride Content (USP)	16.5 – 17.1%
Clarity and Color of Solution (JP)	Passes Test
Identification (IR) (USP-A, EP-B, JP-1)	Conforms to Reference Standard
Loss on Drying (USP/EP/JP)	≤0.20%
pH (1 in 10) (JP)	4.7 – 6.2
Identification, Specific Optical Rotation (USP/EP-A/JP)	+21.5° to +23.5°

The data was analyzed utilizing a shelf-life plot, which determines the point in time at which the slope would exceed the acceptance criteria. As long as the slope has a statistically significant difference from zero using a 95% confidence limit, an estimated time in months can be established at which the acceptance criteria will no longer be met, i.e. the shelf life. This allows BioSpectra to ensure that the product is stable over the time period in which it is part of the stability program. All quantitative data was analyzed using these methods.

The stability program is designed to analyze the stability indicating analyses established for a product in accordance with the Stability Testing Program, BSI-SOP-0136. The specifications for the stability indicating analyses are established in accordance with the Stability Indication Protocol, BSI-SOP-0289, when a new product is manufactured. The study is used to trend the data to determine if there is any significant change over the course of the study to establish the shelf life of the product. This study will be used to establish shelf life for L-Arginine Hydrochloride. The following product codes are commercially available:

- LARH-6350

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2. REFERENCES

2.1. BSI-PRL-0726, Stability Indication Protocol: L-Arginine HCl
2.2. BSI-RPT-1551, Stability Indicating Report: L-Arginine Hydrochloride
2.3. BSI-SOP-0136, Stability Testing Program
2.4. BSI-SOP-0146, Stability Inventory
2.5. BSI-SOP-0289, Stability Indication Protocol
2.6. Current USP
2.7. ICH Q1E

3. SAMPLE DESIGNATION:

Samples placed on the Stability Testing Program consisted of three lots of L-Arginine Hydrochloride packaged into Poly/Poly (P/P) packaging configurations. These samples were packaged in accordance with the Stability Inventory SOP, BSI-SOP-0146. Reference Table 2 for packaging configurations and descriptions. The types of packaging utilized in this stability study were based on BioSpectra final packaging.

TABLE 2: PACKAGING DETAILS

Packaging Configuration	Packaging Description
Poly/Poly (P/P)	Samples are individually placed into small polybags and are sealed with a zip tie. All individual bags are then placed into a poly pail and sealed.

4. STORAGE:

The packaging and storage requirements for L-Arginine Hydrochloride are to be stored in a dry, well-ventilated area away from incompatible substances. For this study, the samples were stored in the Long-Term Stability Chamber H03SC01 at the Bangor, PA facility from February 2024 through February 2025 and will continue until the end of the study in February 2029. Storage conditions have been continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature (25°C ±2°C), mean kinetic temperature (monitor) and relative humidity (60% ±5%). The storage conditions for the time period of this study are detailed in Table 3.

TABLE 3: STORAGE CONDITIONS

Condition	Specification	Value
Minimum Temperature	25°C ±2°C	21.81°C
Maximum Temperature		26.20°C
Average Temperature		25.33°C
Mean Kinetic Temperature	Monitor	25.33°C
Minimum Humidity	60%RH ±5%RH	47.4%
Maximum Humidity		63.4%
Average Humidity		61.2%

Maximum and minimum values that are outside limits for temperature and humidity are due to opening the door of the chamber as explained in Temperature and Humidity Monitoring Assessments for the chambers. Section 5 will include any excursions from these conditions that resulted in an investigation.

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5. INVESTIGATIONS:

5.1. BDI24-126: Out of specification humidity and temperature for H03SC01 occurred on 8/15/24 with a humidity reading of 54.4% and a temperature of 21.81°C. It was discovered that a 20-amp fuse had blown. The fuse was replaced and the chamber went back into specification on 8/16/24 with a humidity reading of 62.3%. There is no impact on the stability samples as this excursion lasted less than 24 hours.

6. LOT EVALUATION:

TABLE 4: S/2309001 P/P

Time Point	Analyses/Specifications							
	Appearance	Assay (Dried Basis)	Chloride Content	Clarity and Color of Solution	Identification (IR)	Loss on Drying	pH (1 in 10)	Specific Optical Rotation
	White or almost white powder or colorless crystals	98.5 – 101.0%	16.5 – 17.1%	Passes Test	Conforms to Reference Standard	≤0.20%	4.7 – 6.2	+21.5° to 23.5°
T_0	White Crystalline Powder	99.84%	16.88%	Passes Test	Conforms to Reference Standard	0.1204%	5.54	+22.58°
T_3	White Crystalline Powder	99.89%	16.85%	Passes Test	Conforms to Reference Standard	0.0635%	5.55	+22.64°
T_6	Almost White Crystalline Powder	99.93%	16.88%	Passes Test	Conforms to Reference Standard	0.1032%	5.56	+22.74°
T_9	Almost White Crystalline Powder	100.20%	16.84%	Passes Test	Conforms to Reference Standard	0.0371%	5.54	+22.63°
T_{12}	Almost White Crystalline Powder	99.83%	16.87%	Passes Test	Conforms to Reference Standard	0.0166%	5.64	+22.50°

- **Remaining Testing Interval Pull Dates**
  - T = 18; Scheduled for August 22, 2025
  - T = 24; Scheduled for February 22, 2026
  - T = 36; Scheduled for February 22, 2027
  - T = 48; Scheduled for February 22, 2028
  - T = 60; Scheduled for February 22, 2029

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TABLE 5: S/2309002 P/P

Time Point	Analyses/Specifications							
	Appearance	Assay (Dried Basis)	Chloride Content	Clarity and Color of Solution	Identification (IR)	Loss on Drying	pH (1 in 10)	Specific Optical Rotation
	White or almost white powder or colorless crystals	98.5 – 101.0%	16.5 – 17.1%	Passes Test	Conforms to Reference Standard	≤0.20%	4.7 – 6.2	+21.5° to 23.5°
T_0	White Powder	100.05%	16.82%	Passes Test	Conforms to Reference Standard	0.0355%	5.57	+22.55°
T_3	White Crystalline Powder	100.04%	16.86%	Passes Test	Conforms to Reference Standard	0.0638%	5.55	+22.62°
T_6	Almost White Crystalline Powder	100.05%	16.79%	Passes Test	Conforms to Reference Standard	0.0755%	5.58	+22.76°
T_9	Almost White Crystalline Powder	100.18%	16.81%	Passes Test	Conforms to Reference Standard	0.0148%	5.55	+22.61°
T_{12}	Almost White Crystalline Powder	99.29%	16.84%	Passes Test	Conforms to Reference Standard	0.0432%	5.58	+22.70°

- **Remaining Testing Interval Pull Dates**
  - T = 18; Scheduled for August 22, 2025
  - T = 24; Scheduled for February 22, 2026
  - T = 36; Scheduled for February 22, 2027
  - T = 48; Scheduled for February 22, 2028
  - T = 60; Scheduled for February 22, 2029

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TABLE 6: S/2309003 P/P

Time Point	Analyses/Specifications							
	Appearance	Assay (Dried Basis)	Chloride Content	Clarity and Color of Solution	Identification (IR)	Loss on Drying	pH (1 in 10)	Specific Optical Rotation
	White or almost white powder or colorless crystals	98.5 – 101.0%	16.5 – 17.1%	Passes Test	Conforms to Reference Standard	≤0.20%	4.7 – 6.2	+21.5° to 23.5°
T_0	White Powder	99.99%	16.92%	Passes Test	Conforms to Reference Standard	0.0452%	5.58	+22.59°
T_3	White Crystalline Powder	99.84%	16.85%	Passes Test	Conforms to Reference Standard	0.0597%	5.53	+22.86°
T_6	Almost White Crystalline Powder	100.09%	16.77%	Passes Test	Conforms to Reference Standard	0.1007%	5.57	+22.73°
T_9	Almost White Crystalline Powder	100.10%	16.85%	Passes Test	Conforms to Reference Standard	0.0314%	5.53	+22.64°
T_{12}	Almost White Crystalline Powder	99.92%	16.82%	Passes Test	Conforms to Reference Standard	0.0106%	5.58	+22.46°

- **Remaining Testing Interval Pull Dates**
  - T = 18; Scheduled for August 22, 2025
  - T = 24; Scheduled for February 22, 2026
  - T = 36; Scheduled for February 22, 2027
  - T = 48; Scheduled for February 22, 2028
  - T = 60; Scheduled for February 22, 2029

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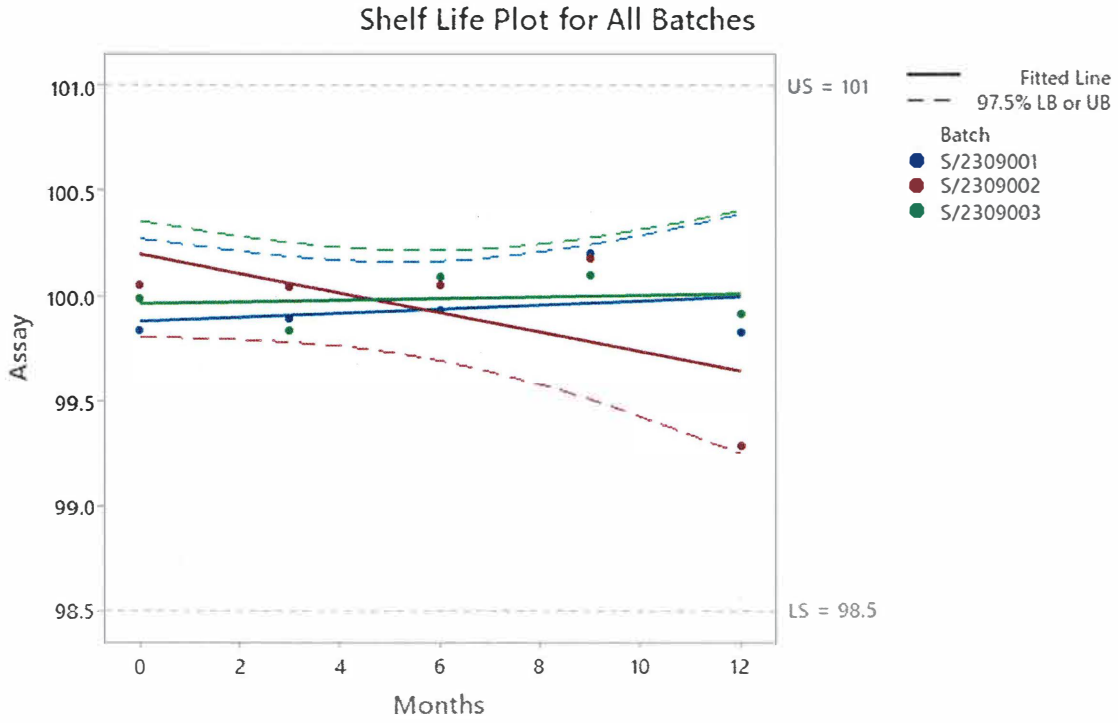

LS = Lower Specification, US = Upper Specification

GRAPH 1: SHELF LIFE PLOTS FOR ASSAY

No shelf-life was able to be determined for Assay (Dried Basis), as the mean response slope is not significantly different from zero using 95% confidence. There is no impact to the product or currently assigned retest period of this material.

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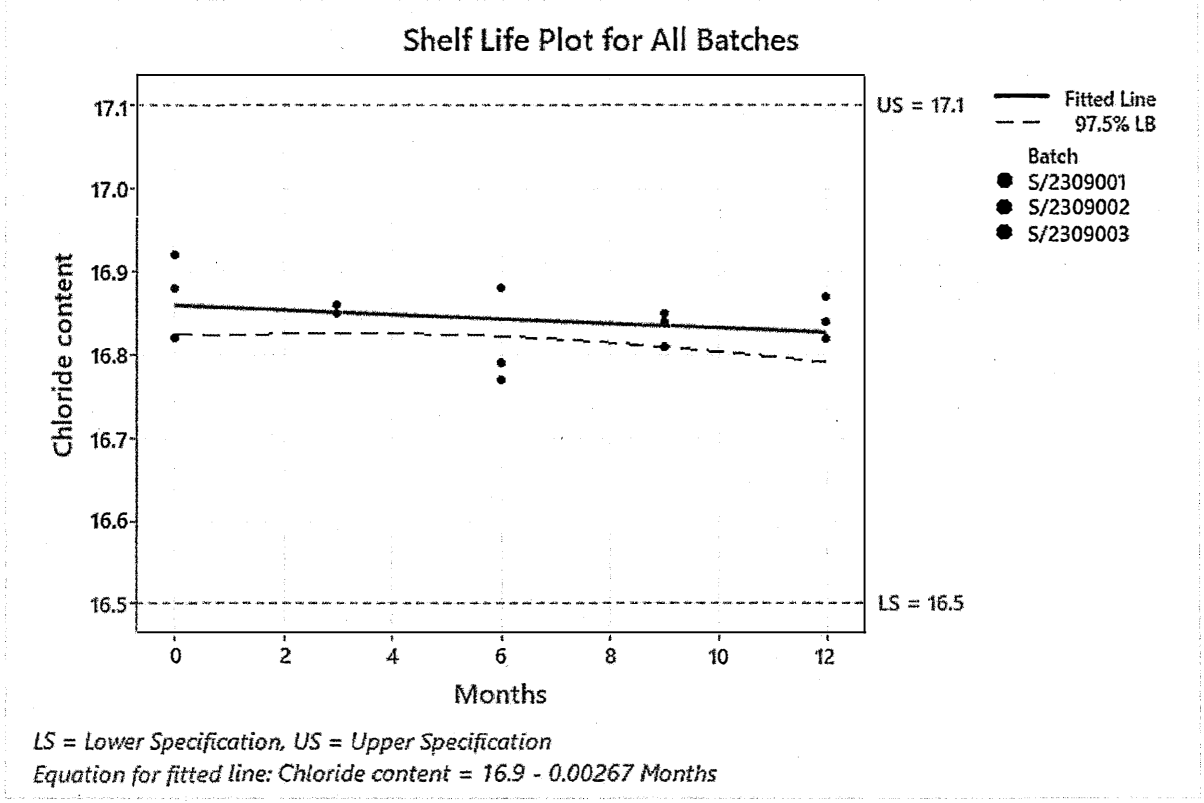

GRAPH 2: SHELF LIFE PLOTS FOR CHLORIDE CONTENT

No shelf-life was able to be determined for Chloride Content as the mean response slope is not significantly different from zero using 95% confidence. There is no impact to the product or currently assigned retest period of this material.

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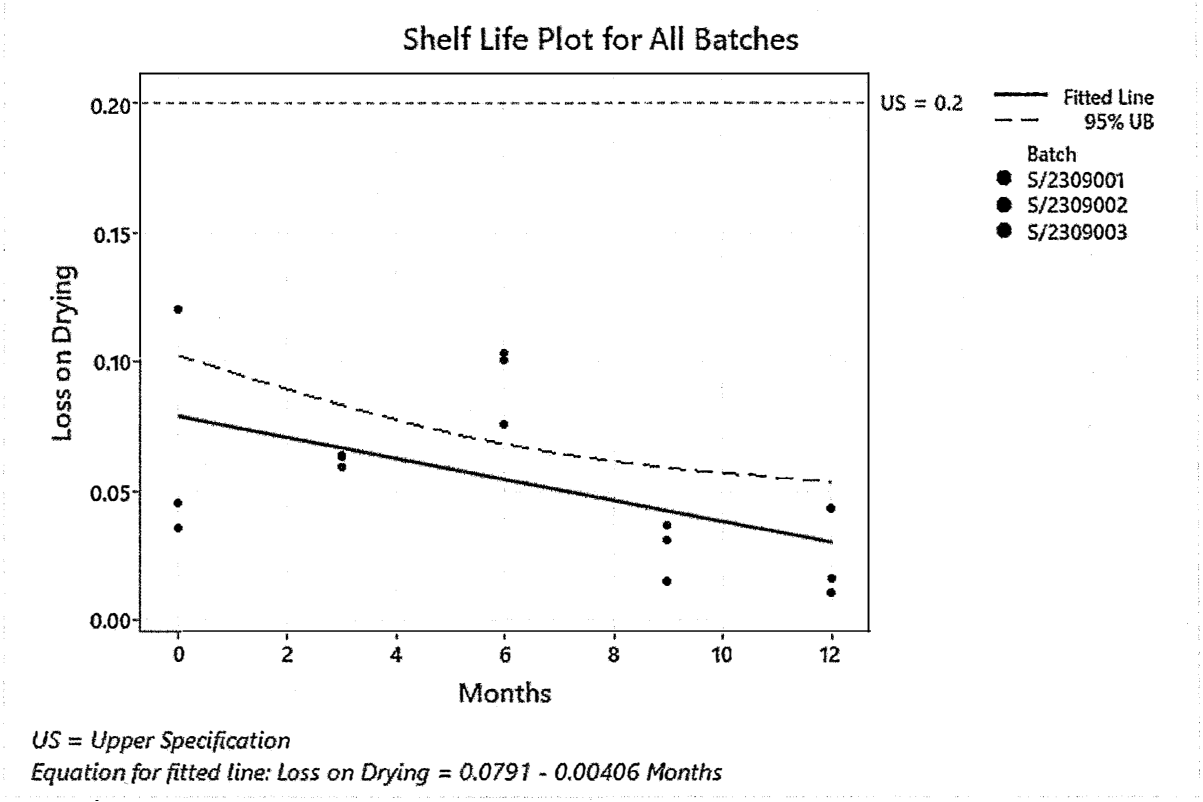

GRAPH 3: SHELF LIFE PLOTS LOSS ON DRYING

No shelf-life was able to be determined for Loss on Drying, as the mean response slope is not significantly different from zero using 95% confidence. There is no impact to the product or currently assigned retest period of this material.

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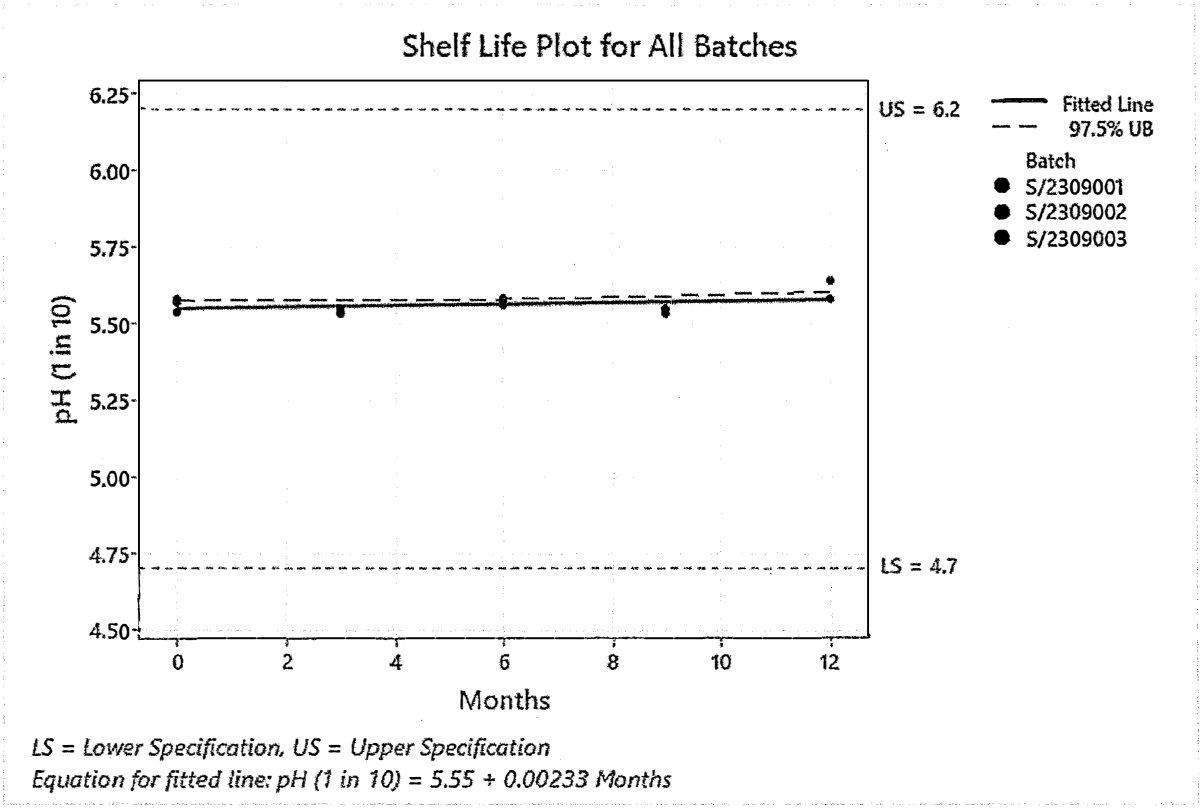

GRAPH 4: SHELF LIFE PLOT FOR PH (1 IN 10)

No shelf-life was able to be determined for pH (1 in 10), as the mean response slope is not significantly different from zero using 95% confidence. There is no impact to the product or currently assigned retest period of this material.

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GRAPH 5: SHELF LIFE PLOT FOR SPECIFIC OPTICAL ROTATION

No shelf-life was able to be determined for Specific Optical Rotation as the mean response slope is not significantly different from zero using 95% confidence. There is no impact to the product or currently assigned retest period of this material.

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7. CONCLUSION:

In regards to the long-term stability study for L-Arginine Hydrochloride, all data met the specifications thus far set forth in the Stability Testing Program for the lots stored at the long-term condition. In accordance with ICH Q1E, the retest date may be proposed for up to 2x, where x is the period covered by long-term stability data, but should be no more than 12 months beyond for long-term conditions (warehouse conditions of 15 – 30°C). The long-term stability study data, along with the predicted shelf-life plots, supports a retest date of 24 months for lots of L-Arginine Hydrochloride.

8. STATEMENT OF COMMITMENT:

8.1. BioSpectra is responsible for the following regarding Stability Data in this report:

8.1.1. In the event that any stability analysis produces results found to be out of specification, the batch produced immediately before and after will be tested in full and analyzed in comparison with the batch in question.

8.1.2. This will serve to provide information to effectively ensure that the root cause of the investigation has not impacted the batch manufactured before or after the batch in question.

8.1.3. If a stability analysis is found to be out of specification, the batch will be withdrawn from the market through communication with the customer. Additionally, an investigation will be conducted to determine the possible withdrawal of the batches produced before and after the batch in question.

8.1.4. In the event that any out of specification results are confirmed, all authorized users of the material will be notified.

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