



100 Majestic Way, Bangor, PA 18013 / www.biospectra.us

URIDINE 2023
VALIDATION LOTS
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 Uridine. 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 manufactured 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 finished good product.

This long-term analysis will assess the stability of Uridine validation lots, manufactured in Process Room N02, URID-0123-00005-PV, URID-0123-00006-PV, and URID-0123-00007-PV that completed nine (9) months of long-term stability in March 2024 and is scheduled to finish at sixty (60) months in July 2028. This study includes the following analyses: Appearance and Color, Identification (IR), Loss on Drying, Melting Point, pH (5%), Transparency (1%), and UV-Assy. Results from all analyses are summarized in Table 2. 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 for 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 all product codes of Uridine. The following Product Codes are commercially available.

- URID-3250

2. REFERENCES:

- 2.1. BSI-SOP-0136, Stability Testing Program
- 2.2. BSI-SOP-0146, Stability Inventory
- 2.3. BSI-SOP-0289, Stability Indication Protocol
- 2.4. Current USP
- 2.5. ICH Q1E

3. SAMPLE DESIGNATION:

- 3.1. Samples initially placed on the stability program for long-term testing consisted of three validation lots of Uridine. Stability samples from these lots were put into both P/P and Labline packaging configuration. The samples were packaged in accordance with the Stability Inventory SOP. Reference Table 1, below, for packaging configuration and description. The type of packaging utilized in this stability study was based on BioSpectra packaging offered to the customer.

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TABLE 1: PACKAGING DETAILS	
Packaging Configuration	Packaging Description
Poly/Poly (P/P)	Samples are individually placed into small polyethylene bags and are sealed with a zip tie. All individual bags are then placed into a poly pail and sealed.
Labline (HDPE Bottle)	Samples are packaged into a HDPE Lab Screw-Top Bottle

4. STORAGE:

4.1. The Packaging and Storage requirements for Uridine are to be in a tightly closed container and stored in a dry, well-ventilated area away from incompatible substances. For the long-term study, the samples were stored in the Long-Term Stability Chamber H03SC01 at the Bangor, PA facility. Storage conditions have been continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature (25°C ±2) and relative humidity (60% ±5). For the time period of June 2023 to March 2024, the maximum temperature recorded was 25.73°C, the minimum temperature recorded was 24.84°C, the average temperature recorded was 25.41°C, and the average mean kinetic temperature was 25.41°C. The maximum relative humidity was 80.5%, the minimum relative humidity was 43.6%, and the average relative humidity was 61.3%. Maximum and minimum values that are outside the limits for temperature and humidity are due to opening the door of the chamber as explained in the Temperature and Humidity Monitoring Assessments for the chamber. Section 5 will include any excursions from these conditions that resulted in an investigation.

5. INVESTIGATIONS:

5.1. **BDI24-13**, Out of range humidity for the Real Time Stability Chamber H03SC01 caused by improper work order completion to prevent water leaking from the stability chamber. On 1/15/24 while conducting a maintenance walkthrough of the Bangor facility water was observed on the floor of room H03RM01. The issue was found to be a faulty pump and later repaired. There was no impact to the current list of materials in the stability chamber.

6. LOT EVALUATION:**TABLE 2A: RESULT OF LONG-TERM STABILITY ANALYSES FOR URID-0123-00005-PV P/P**

Analysis	Specification	T ₀	T ₃	T ₆	T ₉	T ₁₂	T ₁₈	T ₂₄	T ₃₆	T ₄₈	T ₆₀
Appearance and Color	White to almost white powder	White to Almost White Powder	White to Almost White Powder	White to Almost White Powder	White to Almost White Powder	Scheduled for 06/19/24	Scheduled for 12/19/24	Scheduled for 06/19/25	Scheduled for 06/19/26	Scheduled for 06/19/27	Scheduled for 06/19/28
¹ Identification (IR)	Conforms to Spectrum of Reference Standard	CSRS	CSRS	CSRS	CSRS						
Loss on Drying	≤ 0.5%	0.0470%	0.1230%	0.1711%	0.2394%						
² Melting Point	Report 167 - 170°C	167.2 – 168.0°C	167.0 – 168.0°C	167.3 – 168.5°C	167.7 – 168.9°C						
³ pH (5%)	Report 4.0 – 6.0	5.12	5.07	5.10	5.08						
Transparency (1%)	≥ 98.0%	99.8174%	99.7386%	99.5674%	99.6356%						
UV-Assay	≥ 98.0%	99.19%	99.12%	100.0%	100.49%						

¹CSRS = Conforms to Spectrum of Reference Standard

²Analysis (Melting Point) is not required for URID-3250. Specification will be Report, and specification to compare to will be 167 – 170°C.

³Analysis (pH 5%) is not required for URID-3250. Specification will be Report, and the specification to compare to will be 4.0 – 6.0.

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TABLE 2B: RESULT OF LONG-TERM STABILITY ANALYSES FOR URID-0123-00005-PV LABLINE

Analysis	Specification	T ₀	T ₃	T ₆	T ₉	T ₁₂	T ₁₈	T ₂₄	T ₃₆	T ₄₈	T ₆₀
Appearance and Color	White to almost white powder	White to Almost White Powder	White to Almost White Powder	White to Almost White Powder	White to Almost White Powder						
¹ Identification (IR)	Conforms to Spectrum of Reference Standard	CSRS	CSRS	CSRS	CSRS	Scheduled for 06/19/24	Scheduled for 12/19/24	Scheduled for 06/19/25	Scheduled for 06/19/26	Scheduled for 06/19/27	Scheduled for 06/19/28
Loss on Drying	≤ 0.5%	0.0470%	0.1072%	0.1602%	0.1763%						
² Melting Point	Report 167 - 170°C	167.2 – 168.0°C	167.1 – 168.1°C	167.5– 168.6°C	167.7 – 168.8°C						
³ pH (5%)	Report 4.0 – 6.0	5.12	5.06	5.02	5.15						
Transparency (1%)	≥ 98.0%	99.8174%	100.0318%	99.8999%	99.8174%						
UV-Assay	≥ 98.0%	99.19%	98.95%	100.0%	100.11%						

¹CSRS = Conforms to Spectrum of Reference Standard

²Analysis (Melting Point) is not required for URID-3250. Specification will be Report, and specification to compare to will be 167 – 170°C.

³Analysis (pH 5%) is not required for URID-3250. Specification will be Report, and specification to compare to will be 4.0 – 6.0.

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TABLE 2C: RESULT OF LONG-TERM STABILITY ANALYSES FOR URID-0123-00006-PV P/P

Analysis	Specification	T ₀	T ₃	T ₆	T ₉	T ₁₂	T ₁₈	T ₂₄	T ₃₆	T ₄₈	T ₆₀
Appearance and Color	White to almost white powder	White to Almost White Powder	White to Almost White Powder	White to Almost White Powder	White to Almost White Powder						
¹ Identification (IR)	Conforms to Spectrum of Reference Standard	CSRS	CSRS	CSRS	CSRS	Scheduled for 06/19/24	Scheduled for 12/19/24	Scheduled for 06/19/25	Scheduled for 06/19/26	Scheduled for 06/19/27	Scheduled for 06/19/28
Loss on Drying	≤ 0.5%	0.0596%	0.1438%	0.1901%	0.2742%						
² Melting Point	Report 167 - 170°C	167.6 – 168.1°C	167.0 – 167.8°C	167.5 – 168.6°C	167.7 – 169.0°C						
³ pH (5%)	Report 4.0 – 6.0	5.09	5.06	5.07	5.05						
Transparency (1%)	≥ 98.0%	99.7890%	99.9549%	99.4229%	99.7454%						
UV-Assay	≥ 98.0%	99.03%	98.81%	99.3%	100.17%						

¹CSRS = Conforms to Spectrum of Reference Standard

²Analysis (Melting Point) is not required for URID-3250. Specification will be Report, and specification to compare to will be 167 – 170°C.

³Analysis (pH 5%) is not required for URID-3250. Specification will be Report, and specification to compare to will be 4.0 – 6.0.

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TABLE 2D: RESULT OF LONG-TERM STABILITY ANALYSES FOR URID-0123-00006-PV LABLINE

Analysis	Specification	T ₀	T ₃	T ₆	T ₉	T ₁₂	T ₁₈	T ₂₄	T ₃₆	T ₄₈	T ₆₀
Appearance and Color	White to almost white powder	White to Almost White Powder	White to Almost White Powder	White to Almost White Powder	White to Almost White Powder	Scheduled for 06/19/24	Scheduled for 12/19/24	Scheduled for 06/19/25	Scheduled for 06/19/26	Scheduled for 06/19/27	Scheduled for 06/19/28
¹ Identification (IR)	Conforms to Spectrum of Reference Standard	CSRS	CSRS	CSRS	CSRS						
Loss on Drying	≤ 0.5%	0.0596%	0.1393%	0.1415%	0.1918%						
² Melting Point	Report 167 - 170°C	167.6 – 168.1°C	167.1 – 168.1°C	167.6 – 168.6°C	167.9 – 169.1°C						
³ pH (5%)	Report 4.0 – 6.0	5.09	5.07	5.07	5.16						
Transparency (1%)	≥ 98.0%	99.7890%	99.7617%	99.7308%	99.9309%						
UV-Assay	≥ 98.0%	99.03%	99.01%	100.0%	100.30%						

¹CSRS = Conforms to Spectrum of Reference Standard

²Analysis (Melting Point) is not required for URID-3250. Specification will be Report, and specification to compare to will be 167 – 170°C.

³Analysis (pH 5%) is not required for URID-3250. Specification will be Report, and specification to compare to will be 4.0 – 6.0.

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TABLE 2E: RESULT OF LONG-TERM STABILITY ANALYSES FOR URID-0123-00007-PV P/P

Analysis	Specification	T ₀	T ₃	T ₆	T ₉	T ₁₂	T ₁₈	T ₂₄	T ₃₆	T ₄₈	T ₆₀
Appearance and Color	White to almost white powder	White to Almost White Powder	White to Almost White Powder	White to Almost White Powder	White to Almost White Powder						
¹ Identification (IR)	Conforms to Spectrum of Reference Standard	CSRS	CSRS	CSRS	CSRS	Scheduled for 06/19/24	Scheduled for 12/19/24	Scheduled for 06/19/25	Scheduled for 06/19/26	Scheduled for 06/19/27	Scheduled for 06/19/28
Loss on Drying	≤ 0.5%	0.1018%	0.1887%	0.1471%	0.2127%						
² Melting Point	Report 167 - 170°C	167.6 – 168.1°C	167.0 – 168.0°C	167.5 – 168.6°C	167.8 – 169.1°C						
³ pH (5%)	Report 4.0 – 6.0	5.02	5.08	5.09	5.10						
Transparency (1%)	≥ 98.0%	99.8593%	99.9472%	99.6335%	99.8334%						
UV-Assay	≥ 98.0%	98.83%	100.4%	99.8%	100.07%						

¹CSRS = Conforms to Spectrum of Reference Standard

²Analysis (Melting Point) is not required for URID-3250. Specification will be Report, and specification to compare to will be 167 – 170°C.

³Analysis (pH 5%) is not required for URID-3250. Specification will be Report, and specification to compare to will be 4.0 – 6.0.

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TABLE 2F: RESULT OF LONG-TERM STABILITY ANALYSES FOR URID-0123-00007-PV LABLINE

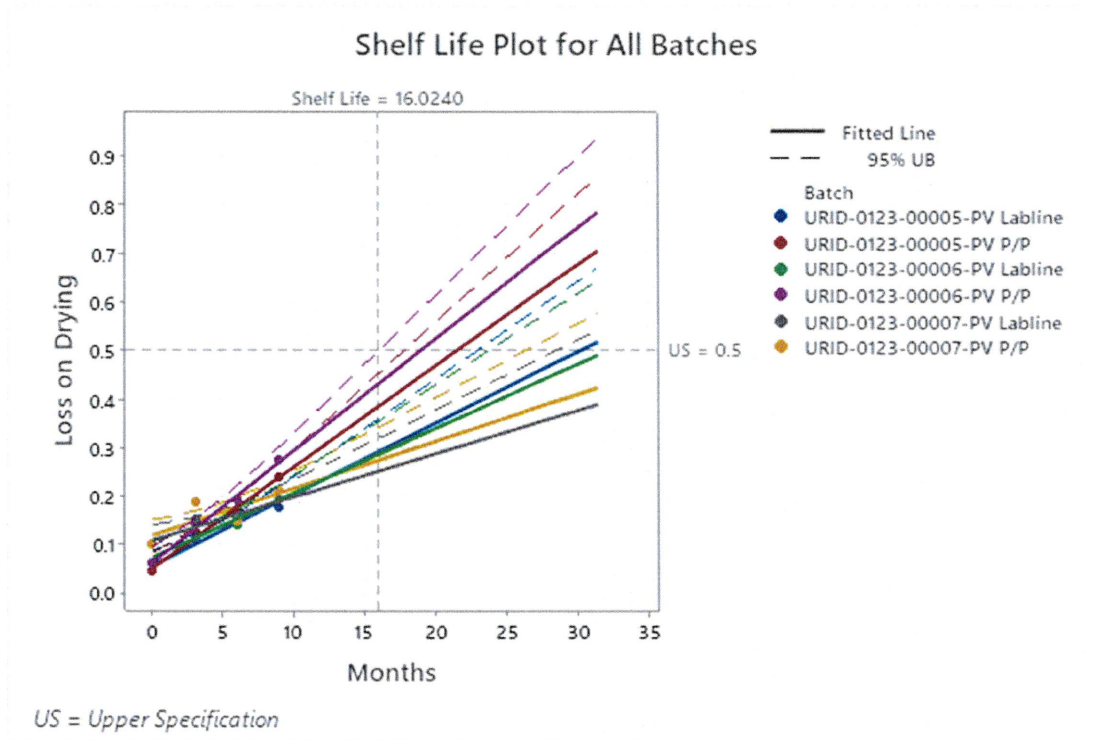
Analysis	Specification	T ₀	T ₃	T ₆	T ₉	T ₁₂	T ₁₈	T ₂₄	T ₃₆	T ₄₈	T ₆₀
Appearance and Color	White to almost white powder	White to Almost White Powder	White to Almost White Powder	White to Almost White Powder	White to Almost White Powder	Scheduled for 06/19/24	Scheduled for 12/19/24	Scheduled for 06/19/25	Scheduled for 06/19/26	Scheduled for 06/19/27	Scheduled for 06/19/28
¹ Identification (IR)	Conforms to Spectrum of Reference Standard	CSRS	CSRS	CSRS	CSRS						
Loss on Drying	≤ 0.5%	0.1018%	0.1530%	0.1468%	0.1932%						
² Melting Point	Report 167 - 170°C	167.6 – 168.1°C	167.2 – 168.1°C	167.5 – 168.6°C	167.8 – 168.9°C						
³ pH (5%)	Report 4.0 – 6.0	5.02	5.08	5.07	5.05						
Transparency (1%)	≥ 98.0%	99.8593%	99.9895%	99.3662%	99.9679%						
UV-Assay	≥ 98.0%	98.83%	100.0%	100.2%	99.83%						

¹CSRS = Conforms to Spectrum of Reference Standard

²Analysis (Melting Point) is not required for URID-3250. Specification will be Report, and specification to compare to will be 167 – 170°C.

³Analysis (pH 5%) is not required for URID-3250. Specification will be Report, and specification to compare to will be 4.0 – 6.0.

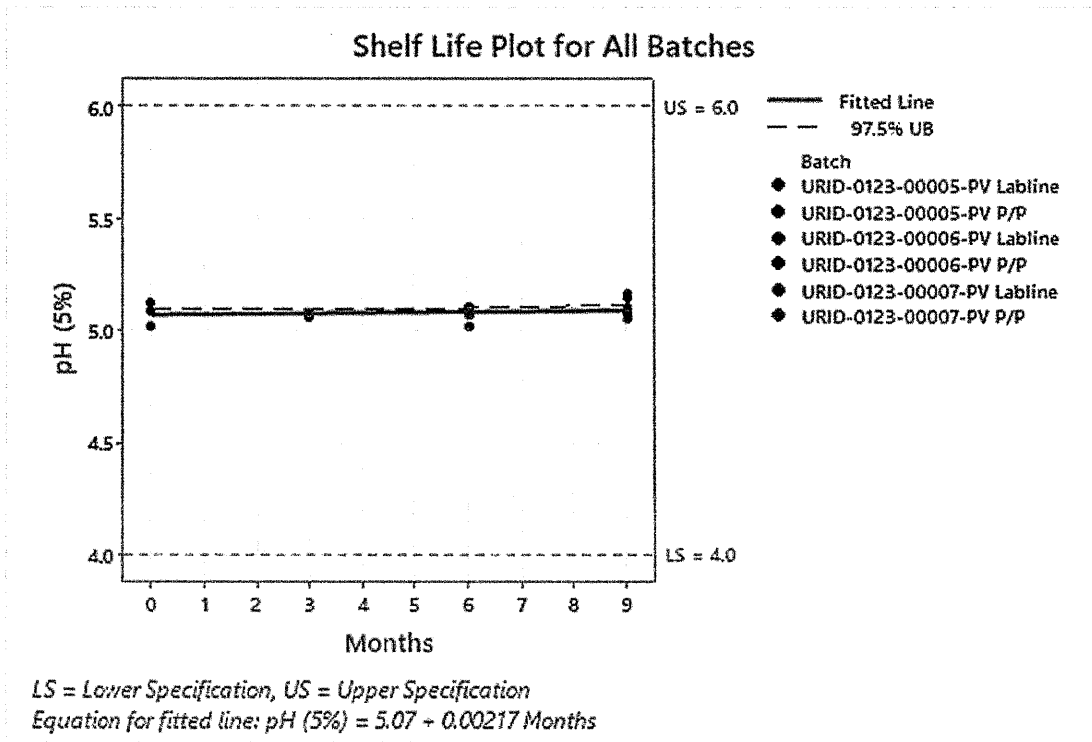
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GRAPH 1: LONG TERM LOSS ON DRYING

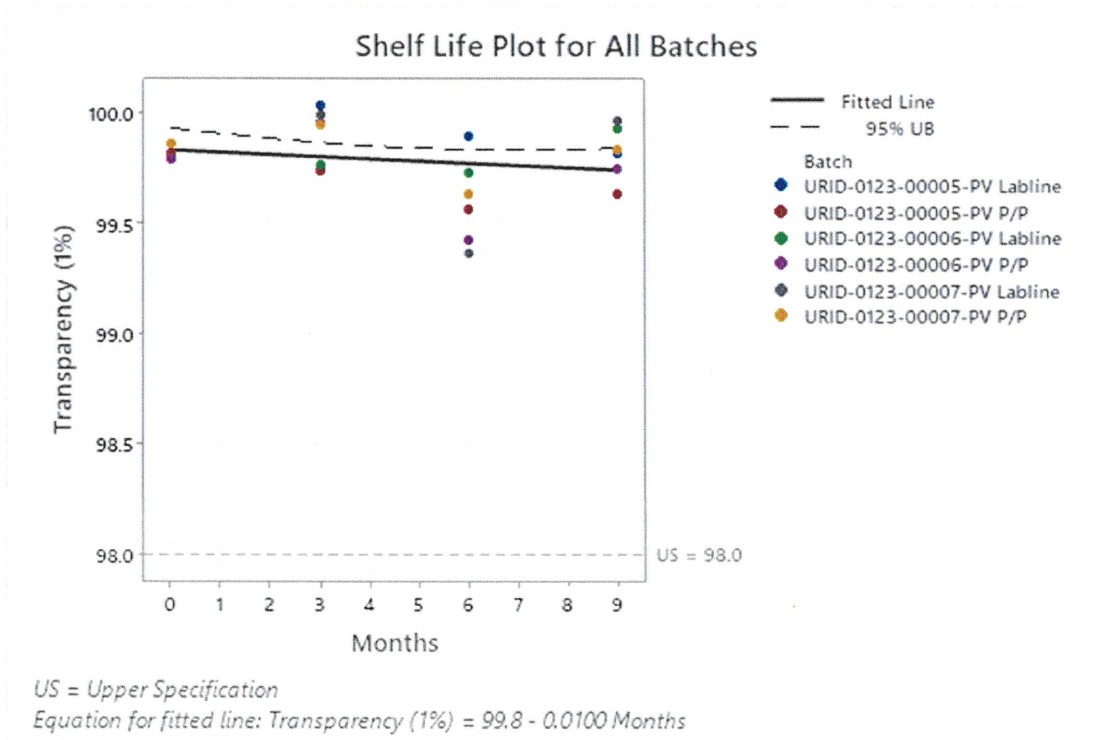
The predicted Shelf-Life for the Long-Term Loss on Drying was determined to be 16.0240 months at the T=9-month time interval. Results will continue to be monitored. There is no impact to the product or currently assigned retest period of this material.

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GRAPH 2: LONG TERM PH (5%)

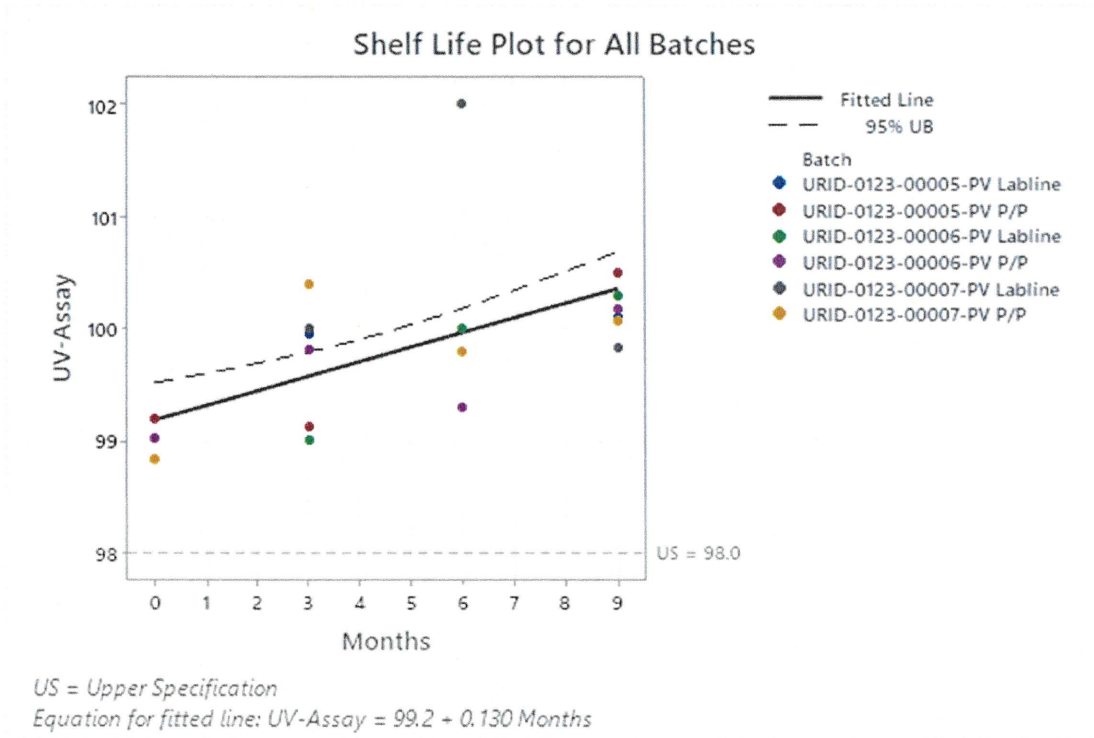
No Shelf-Life was able to be determined for the Long-Term pH (5%), as the mean response slope is not significantly different from zero using 95% confidence at the T=9-month time interval. There is no impact to the product or currently assigned retest period of this material. There is no specification for pH (5%) for this product, but there is a monitored range of 4.0 – 6.0. As per BDI22-224, the data “will not be used to calculate a shelf-life trending plot” a shelf life plot was generated for informational purposes.



GRAPH 3: LONG TERM TRANSPARENCY (1%)

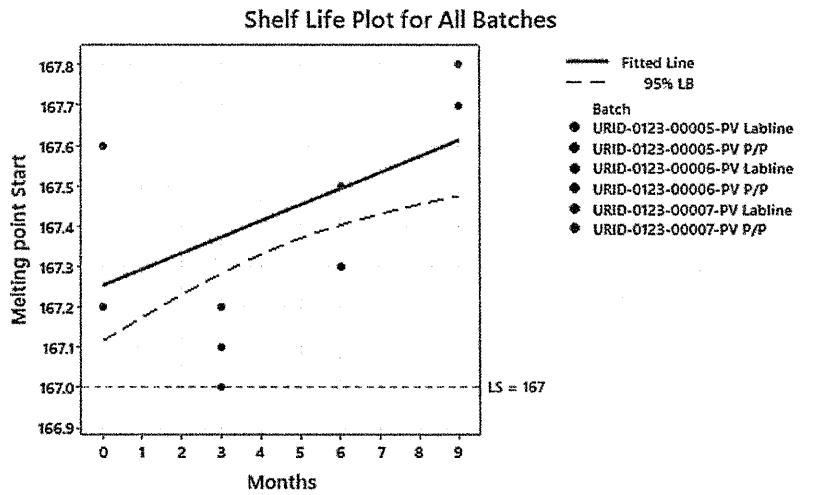
No Shelf-Life was able to be determined for the Long-Term Transparency (1%), as the mean response slope is not significantly different from zero using 95% confidence at the T=9-month time interval. Results will continue to be monitored. There is no impact to the product or currently assigned retest period of this material.

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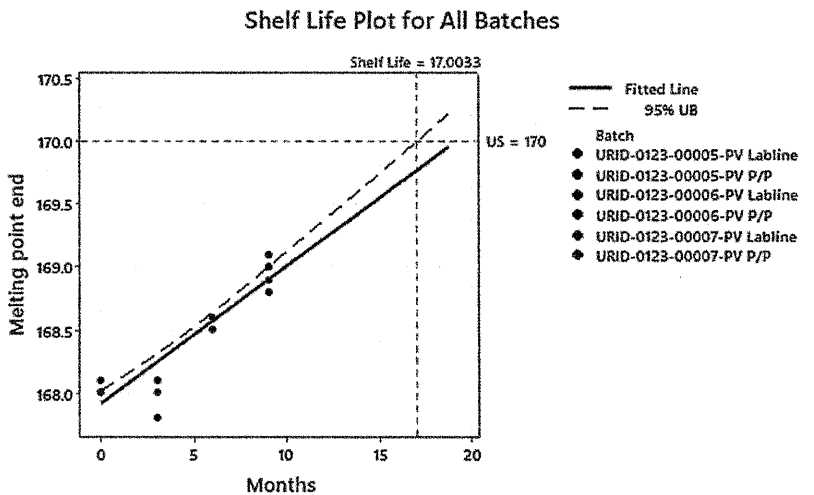


GRAPH 4: LONG TERM UV-ASSAY

No Shelf-Life was able to be determined for the Long-Term UV-Assay, as the mean response slope is not significantly different from zero using 95% confidence at the T=9-month time interval. Results will continue to be monitored. There is no impact to the product or currently assigned retest period of this material.



LS = Lower Specification
 Equation for fitted line: $\text{Melting point Start} = 167 + 0.0400 \text{ Months}$



US = Upper Specification
 Equation for fitted line: $\text{Melting point end} = 168 + 0.109 \text{ Months}$

GRAPH 5: LONG TERM MELTING POINT

No Shelf-Life was able to be determined for Melting Point Start, as the mean response slope is not significantly different from zero using 95% confidence at the T=9-month time interval. Results will continue to be monitored. There is no impact to the product or currently assigned retest period of this material. The predicted Shelf-Life for Long-Term Melting Point End was determined to be 17.0033 months at the T=9-month time interval. Results will continue to be monitored. There is no impact to the product or currently assigned retest period of this material.

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7. CONCLUSION:

- 7.1. All data met the specifications set forth in the Stability Testing Program. 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. Long-term Stability Data displayed in this report up to 9 months for Uridine manufactured at BioSpectra in the Bangor, PA facility, along with the predicted shelf-life plots, the results continue to support the already established retest date. The lots manufactured in 2023 preliminary data is supporting a retest date of 16 months, however the retest date will remain 24 months with an extension to 30 months upon request based on the stability study with more time interval data points, BSI-RPT-1231. Samples have met specifications as of $T=9$ (9 months) and will continue to be monitored.

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.

Signature Manifest**Document Number:** BSI-RPT-1784**Revision:** 1.1**Title:** Uridine 2023 Validation Lots Long Term Stability Report**Effective Date:** 04 Jun 2024

All dates and times are in US/Eastern.

BSI-RPT-1784 Uridine 2023 Validation Lots Long Term Stability Report**Change Request**

Name/Signature	Title	Date	Meaning/Reason
Amy Yencho (AMY.YENCHO)	Vice President of Laboratory Services	30 May 2024, 11:58:37 AM	Approved
Catherine Smith (CATHERINE.SMITH)	Document Control Technician III	30 May 2024, 12:07:25 PM	Approved

Originator and Peer Review Collaboration Workspace

Name/Signature	Title	Date	Meaning/Reason
Stephen Hrizuk (STEPHEN.HRIZUK)	Stability Manager	30 May 2024, 02:31:55 PM	Complete & Quit
Carissa Albert (CARISSA.ALBERT)	Senior Quality Manager, Majestic & Jacobsburg	30 May 2024, 03:47:14 PM	Complete & Quit
Emily Gibbons (EMILY.GIBBONS)	Laboratory Systems Supervisor, Rockdale	31 May 2024, 08:57:19 AM	Complete & Quit
Wayne Talamonti (WAYNE.TALAMONTI)	Director of Laboratory Systems	31 May 2024, 09:01:26 AM	Complete

Departmental Approval

Name/Signature	Title	Date	Meaning/Reason
Amy Yencho (AMY.YENCHO)	Vice President of Laboratory Services	03 Jun 2024, 11:25:14 AM	Approved

Author Approval

Name/Signature	Title	Date	Meaning/Reason
Wayne Talamonti (WAYNE.TALAMONTI)	Director of Laboratory Systems	31 May 2024, 01:03:52 PM	Approved

Quality Approval

Name/Signature	Title	Date	Meaning/Reason
Carissa Albert (CARISSA.ALBERT)	Senior Quality Manager, Majestic & Jacobsburg	04 Jun 2024, 08:54:25 AM	Approved

Set Date

Name/Signature	Title	Date	Meaning/Reason
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Catherine Smith
(CATHERINE.SMITH)

Document Control Technician III

04 Jun 2024, 01:31:12 PM

Approved