BIOSPECTRA
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URIDINE 2022VALIDATION 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 report will assess the stability data of Uridine validation lots, manufactured in process room N05, URID-0122-00005-PV, URID-0122-00006-PV and URID-0122-00007-PV that completed eighteen (18) months of long-term stability in January 2024 and is scheduled to finish at sixty (60) months in July 2027. 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 Tables 2 through 7. 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 code is 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 real time 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.

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), relative humidity (60%RH ±5) and mean kinetic temperature (monitor). For the time period of July 2022 to January 2024, the maximum temperature recorded was 25.73°C, the minimum temperature recorded was 24.84°C, the average temperature recorded was 25.44°C, and the average mean kinetic temperature was 25.44°C. The maximum relative humidity was 80.5%, the minimum relative humidity was 43.6%, and the average relative humidity was 61.7%. 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. **BLI22-31**: This Laboratory investigation documents Out of Specification (OOS) and Out of Trend (OOT) data for UV Assay for URID-0122-00006-PV T=3 samples for all conditions and packaging configurations. The root cause for this investigation was attributed to sample preparation error as multiple dilutions were required. The method was optimized to reduce error. The six retests performed by two analysts refuted the original OOS and OOT results. The average of the six retests were implemented as the official results.

5.2. **BDI22-224**: Testing for pH (5%) was not complete for the T=0 timepoint for all three lots of Uridine. This test was not required for finished goods (URID-3250) or for the Degradation and Impurity Profile Report: Uridine (Excipient) (BSI-RPT-1005). Testing was not requested for stability, and therefore, it was not completed. There is no specification for pH (5%) and the data is only for monitoring purposes.

5.3. **BLI23-26**: Laboratory investigation documents Out of Specification (OOS) data for UV Assay for URID-0122-00005-PV P/P T=12 samples for and URID-0122-00005-PV Labline T=12 packaging configurations. The root cause for this investigation was attributed to sample preparation error. The six retests performed by two analysts refuted the original OOS results. The average of the six retests were implemented as the official results.

5.4. **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 2: RESULT OF LONG-TERM STABILITY ANALYSES FOR URID-0122-00005-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 Powder	White to Almost White Powder	White to Almost White Powder	White to Almost White Powder	White Powder	White to Almost White Powder	Scheduled for 07/05/24	Scheduled for 07/05/25	Scheduled for 07/05/26	Scheduled for 07/05/27
[1]Identification (IR)	Conforms to Spectrum of Reference Standard	CSRS	CSRS	CSRS	CSRS	CSRS	CSRS				
Loss on Drying	≤ 0.5%	0.0856%	0.2009%	0.2403%	0.2315%	0.2116%	0.2096%				
[2]Melting Point	Report 167 - 170°C	167.1 – 168.5°C	167.7 – 168.9°C	167.6 – 168.6°C	168.5 – 169.8°C	173.0 – 174.5°C	167.4 – 168.7°C				
[3]pH (5%)	Report 4.0 – 6.0	Refer to BDI22-224	5.19	5.10	5.11	5.09	5.09				
Transparency (1%)	≥ 98.0%	99.6384%	99.3873%	99.7030%	99.5441%	99.5538%	99.5670%				
UV-Assay	≥ 98.0%	98.35%	99.78%	99.15%	98.98%	98.98%	99.53%				

[1]CSRS = Conforms to Spectrum of Reference Standard

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

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

TABLE 3: RESULT OF LONG-TERM STABILITY ANALYSES FOR URID-0122-00005-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 Powder	White to Almost White Powder	White to Almost White Powder	White to Almost White Powder	White Powder	White to Almost White Powder	Scheduled for 07/05/24	Scheduled for 07/05/25	Scheduled for 07/05/26	Scheduled for 07/05/27
[1]Identification (IR)	Conforms to Spectrum of Reference Standard	CSRS	CSRS	CSRS	CSRS	CSRS	CSRS				
Loss on Drying	≤ 0.5%	0.0856%	0.1476%	0.1529%	0.1722%	0.1797%	0.1906%				
[2]Melting Point	Report 167 - 170°C	167.1 – 168.5°C	167.8 – 169.2°C	167.7 – 168.8°C	168.3 – 169.6°C	172.9 – 174.5°C	167.5 – 168.5°C				
[3]pH (5%)	Report 4.0 – 6.0	Refer to BDI22-224	5.31	5.13	5.09	5.10	5.10				
Transparency (1%)	≥ 98.0%	99.6384%	99.2864%	99.8277%	99.5450%	99.7323%	99.7069%				
UV-Assay	≥ 98.0%	98.35%	100.11%	99.26%	99.03%	98.50%	99.54%				

[1]CSRS = Conforms to Spectrum of Reference Standard

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

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

TABLE 4: RESULT OF LONG-TERM STABILITY ANALYSES FOR URID-0122-00006-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	Almost white powder	White to Almost White Powder	White to Almost White Powder	White to Almost White Powder	White to Almost White Powder	White Powder	Scheduled for 07/12/24	Scheduled for 07/12/25	Scheduled for 07/12/26	Scheduled for 07/12/27
[1]Identification (IR)	Conforms to Spectrum of Reference Standard	CSRS	CSRS	CSRS	CSRS	CSRS	CSRS				
Loss on Drying	≤ 0.5%	0.0292%	0.1510%	0.1530%	0.1875%	0.1814%	0.1745%				
[2]Melting Point	Report 167 - 170°C	167.1 – 168.5°C	167.6 – 168.8°C	167.5 – 168.9°C	168.0 – 169.3°C	167.1 – 167.8°C	167.4 – 168.3°C				
[3]pH (5%)	Report 4.0 – 6.0	Refer to BDI22-224	5.22	5.15	5.16	5.17	5.15				
Transparency (1%)	≥ 98.0%	99.7055%	99.6776%	99.5854%	99.6147%	99.7181%	99.7726%				
UV-Assay	≥ 98.0%	100.09%	99.24%	99.75%	99.58%	98.84%	98.64%				

[1]CSRS = Conforms to Spectrum of Reference Standard

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

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

TABLE 5: RESULT OF LONG-TERM STABILITY ANALYSES FOR URID-0122-00006-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	Almost white powder	White to Almost White Powder	White to Almost White Powder	White to Almost White Powder	White to Almost White Powder	White Powder	Scheduled for 07/12/24	Scheduled for 07/12/25	Scheduled for 07/12/26	Scheduled for 07/12/27
[1]Identification (IR)	Conforms to Spectrum of Reference Standard	CSRS	CSRS	CSRS	CSRS	CSRS	CSRS				
Loss on Drying	≤ 0.5%	0.0292%	0.1129%	0.1626%	0.1841%	0.2022%	0.0710%				
[2]Melting Point	Report 167 - 170°C	167.1 – 168.5°C	167.7 – 168.6°C	167.5 – 168.8°C	168.1 - 169.5°C	167.1 – 168.2°C	167.4 – 168.3°C				
[3]pH (5%)	Report 4.0 – 6.0	Refer to BDI22-224	5.20	5.18	5.15	5.16	5.15				
Transparency (1%)	≥ 98.0%	99.7055%	99.8020%	99.5059%	99.6433%	99.8054%	99.7926%				
UV-Assay	≥ 98.0%	100.09%	99.50%	100.38%	99.30%	98.86%	99.38%				

[1]CSRS = Conforms to Spectrum of Reference Standard

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

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

TABLE 6: RESULT OF LONG-TERM STABILITY ANALYSES FOR URID-0122-00007-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	White to Almost White Powder	White to Almost White Powder	Scheduled for 07/14/24	Scheduled for 07/14/25	Scheduled for 07/14/26	Scheduled for 07/14/27
[1]Identification (IR)	Conforms to Spectrum of Reference Standard	CSRS	CSRS	CSRS	CSRS	CSRS	CSRS				
Loss on Drying	≤ 0.5%	0.1123%	0.1714%	0.2142%	0.2069%	0.2155%	0.1938%				
[2]Melting Point	Report 167 - 170°C	167.1 – 168.5°C	167.3 – 168.6°C	167.5 – 168.8°C	168.3 – 169.8°C	167.1 – 168.0°C	168.0 – 169.0°C				
[3]pH (5%)	Report 4.0 – 6.0	Refer to BDI22-224	5.25	5.25	5.20	5.22	5.22				
Transparency (1%)	≥ 98.0%	99.3303%	99.5041%	98.9688%	99.2636%	99.3820%	99.4615%				
UV-Assay	≥ 98.0%	99.79%	99.15%	99.47%	99.05%	98.83%	99.20%				

[1]CSRS = Conforms to Spectrum of Reference Standard

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

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

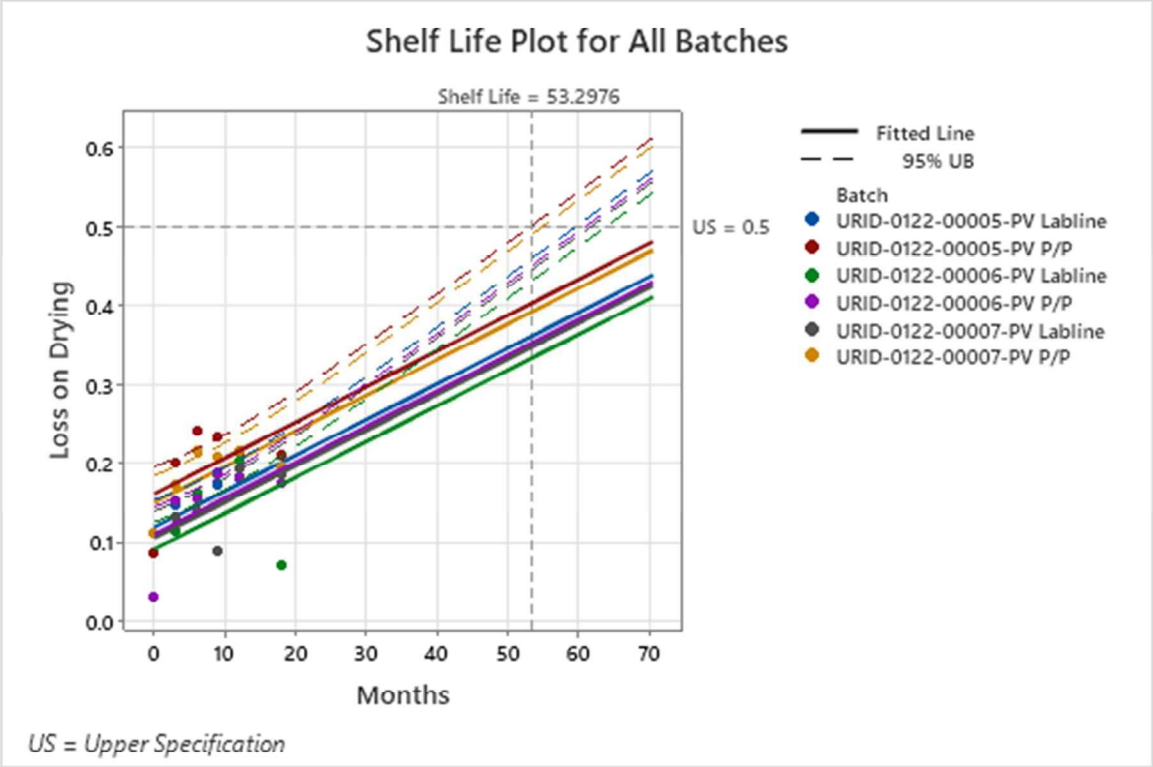
TABLE 7: RESULT OF LONG-TERM STABILITY ANALYSES FOR URID-0122-00007-PV LABLINE

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	White to Almost White Powder	White to Almost White Powder	Scheduled for 07/14/24	Scheduled for 07/14/25	Scheduled for 07/14/26	Scheduled for 07/14/27
[1]Identification (IR)	Conforms to Spectrum of Reference Standard	CSRS	CSRS	CSRS	CSRS	CSRS	CSRS				
Loss on Drying	≤ 0.5%	0.1123%	0.1308%	0.1387%	0.0879%	0.1918%	0.1852%				
[2]Melting Point	Report 167 - 170°C	167.1 – 168.5°C	167.4 – 168.6°C	167.4 – 168.8°C	168.1 – 169.6°C	167.2 – 168.0°C	167.5 – 168.9°C				
[3]pH (5%)	Report 4.0 – 6.0	Refer to BDI22-224	5.27	5.20	5.22	5.24	5.21				
Transparency (1%)	≥ 98.0%	99.3303%	99.5060%	98.7964%	99.3676%	99.4323%	99.4653%				
UV-Assay	≥ 98.0%	99.79%	100.57%	99.36%	98.92%	98.95%	99.50%				

[1]CSRS = Conforms to Spectrum of Reference Standard

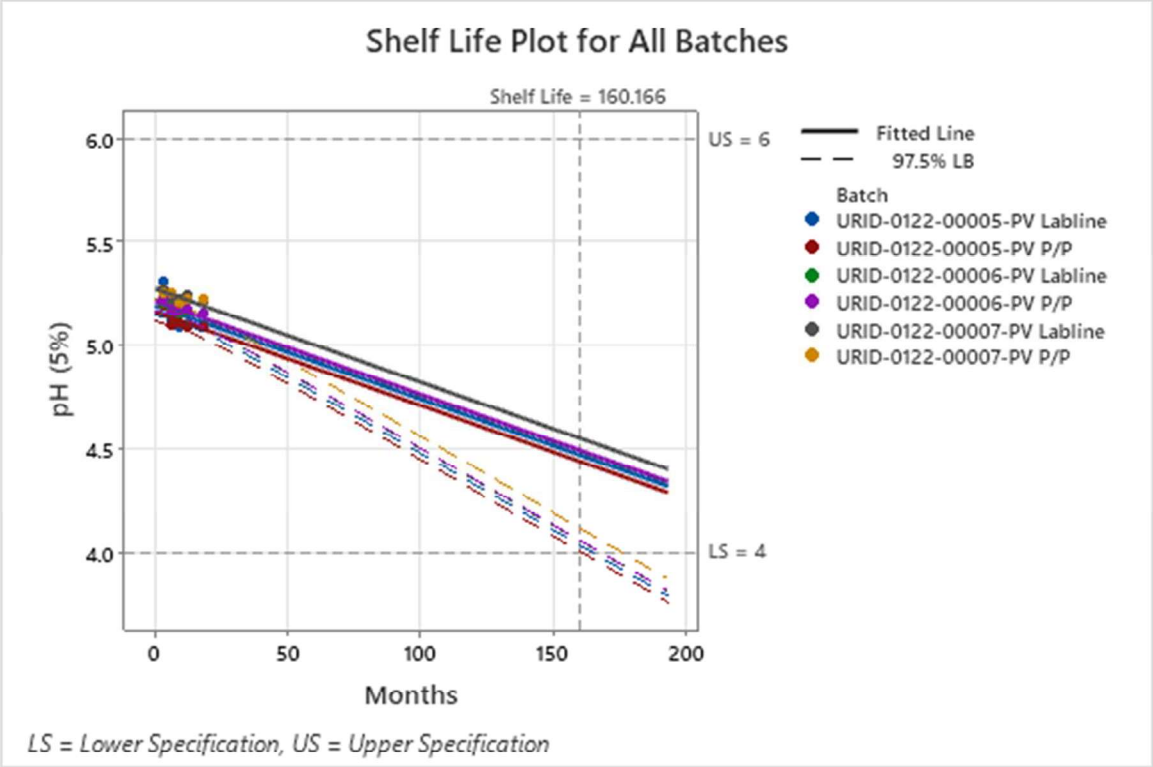
[2]Analysis (Melting Point) is not required for URID-3250. Specification will be Report, and specification to compare to will be 167 – 170°C.

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



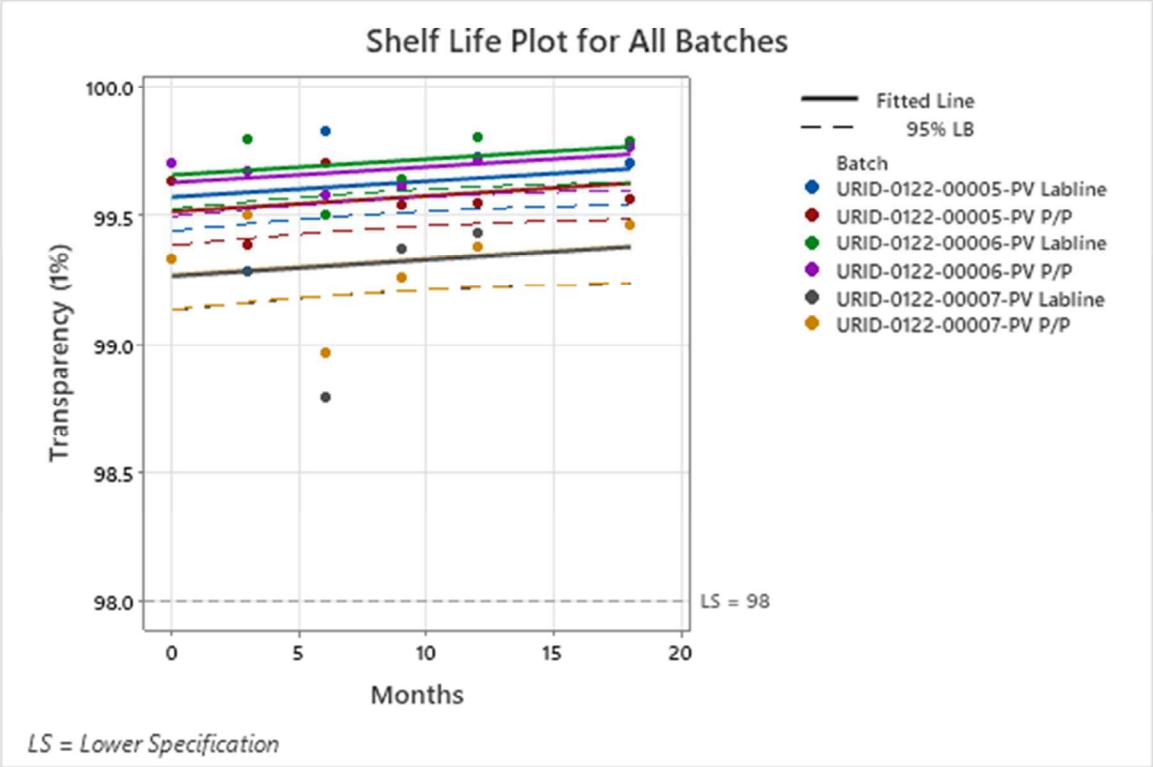
GRAPH 1: LONG-TERM LOSS ON DRYING

The predicted Shelf-Life for Long-Term Loss on Drying was determined to be 53.2976 months at the T=18-month time interval. Results will continue to be monitored. There is no impact to the product or currently assigned retest period of this material.



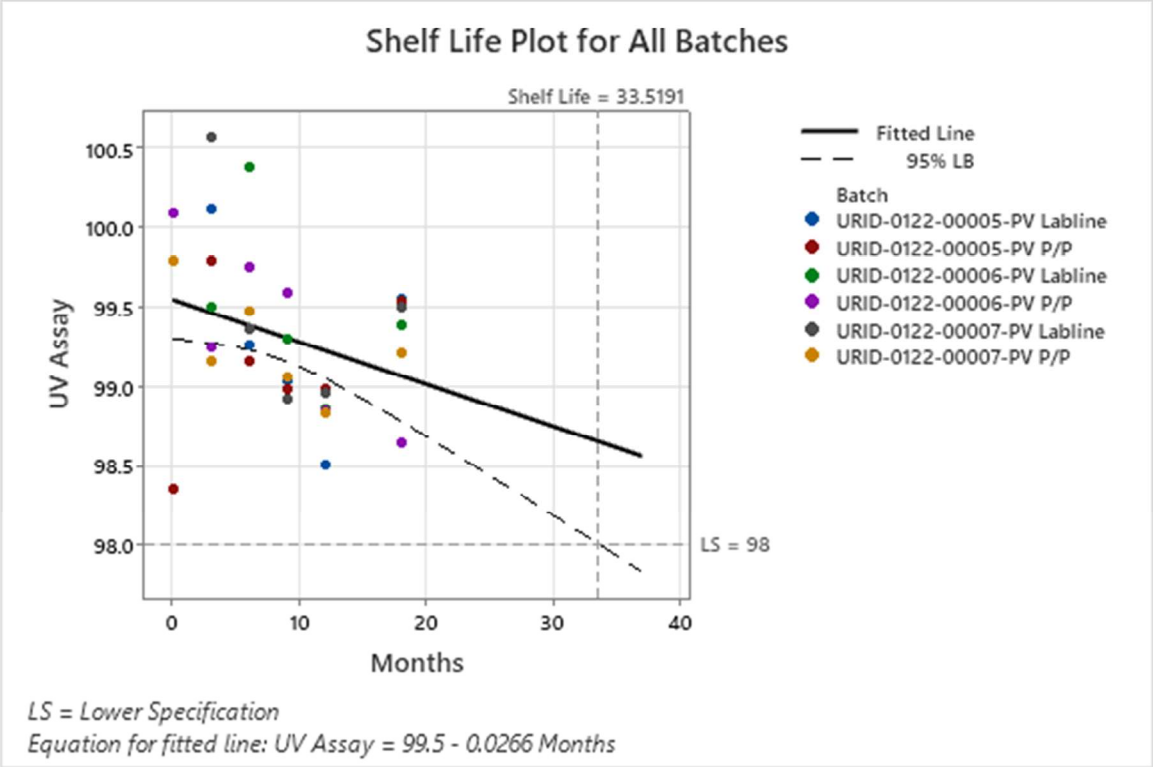
GRAPH 2: LONG-TERM PH (5%)

The predicted Shelf-Life for Long-Term pH (5%) was determined to be 160.166 months at the T=18-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 T=0 was not tested for these lots as a finished good specification, therefore only T=3 through T=18 data available. 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 Long-Term Transparency (1%), as the mean response slope is not significantly different from zero using 95% confidence at the T=18-month time interval. Results will continue to be monitored. There is no impact to the product or currently assigned retest period of this material.



GRAPH 4: LONG-TERM UV-ASSAY

The predicted Shelf-Life for Long-Term UV Assay was determined to be 33.5191 months at the T=18-month time interval. Results will continue to be monitored. There is no impact to the product or currently assigned retest period of this material.

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 real time conditions. Long-Term Stability Data displayed in this report up to 18 months for Uridine manufactured at BioSpectra in the Bangor, PA facility, along with the predicted shelf-life plots, would support a retest date of 24 months, with an extension to a retest date of 30 months upon request and will continued to be evaluated. Samples have met specifications as of T=18 (18 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.