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6N HCL IN IPA
REAL-TIME STABILITY REPORT:
IH4101-005-0517

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1. OVERVIEW:

The purpose of this report is to analyze the data obtained from the Real-Time Stability of 6N HCl in IPA manufactured at BioSpectra's Bangor, PA facility. Samples were placed on the Stability Testing Program in May 2017, to fulfil the requirements of adding one GMP manufactured batch per year. The long-term Real-Time Stability Program consists of testing every three months for the first year, every six months for the second year and annually for each subsequent year, notated as T_n, where *n* represents the number of months on stability. Analysis has been conducted for a total of thirty-six months in order to assure that the manufactured material remains stable under the specified conditions and for the specified interval of time. The analysis of the compiled data may be used to re-evaluate the retest period for future lots of manufactured material.

This Real-Time Stability analysis assesses the stability of one lot of 6N HCl in IPA that completed three years of long-term stability in May 2020. The study included the following analyses: Appearance and Color, Normality, and Identification (IR). Results from all analyses are summarized in Table 1.

The assay 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 Predicted Shelf Life. This allows BioSpectrato ensure that the product will be stable over the time period in which it is part of the Stability Testing Program.

2. REFERENCES:

2.1 Current USP
2.2 ICH Q1
2.3 Stability Testing Program
2.4 Stability Inventory

3. SAMPLE DESIGNATION:

Samples placed on the Stability Testing Program consisted of one lot of 6N HCl in IPA for the year 2017. Stability samples were initially placed into 100mL black HDPE bottles. This packaging configuration is denoted as 100 mL HDPE Bottle. At the time of T_3 analysis, it was noted that most of the samples had evaporated from the bottles. It was determined through BLI17-40 that this packaging is unsuitable for 6N HCl in IPA. The remainder of the stability study was performed using a partial 55- gallon black poly drum of material that was left over from manufacturing.

4. STORAGE:

It should be noted that there is no temperature specification for the storage of this material. Initially, this 6N HCl in IPA lot was stored in the Bangor QC Stability cage in the Zone M Warehouse. At the time of T_3 analysis, it was noted that most of the samples had evaporated from the bottles. It was determined through BLI17-40 that this material should be placed in Cold Storage. There is no temperature data available for this storage location for this time period.

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For the remainder of this stability study, the material was stored in Refrigerated Storage Containers which have a temperature specification of 2°C - 8°C. The material was mostly stored in A01CR02, but for a very short period of time, the material had to be moved to A01RC04, refer to BDI19-145 and BTOI19-70. There is no temperature data available for A01RC04 during this time.

There is no temperature data available for A01RC01 prior to April 2018. From April 2018 through the end of the study, the temperature was monitored consistently, using tempmate single use data loggers which record for 110 days. The minimum temperature reached in the storage container during thistime was -3.7°C. The maximum temperature reached in the storage container during this time was 23.1. No discrepancy was issued for this temperature excursion.

5. INVESTIGATIONS:

- BLI17-40: An out of specification Assay result was obtained for the T_3 stability sample. It was concluded that stability samples were being stored in improper packaging. A partial drum of this material was given to Quality Control for the remainder of the stability study.

- BDI18-91: Data loggers recorded temperatures outside the specified range on 8/23/18. The temperature excursions were found during the review of the cold storage temperature data. There is no risk to the material, as there is no temperature specification for 6N HCl in IPA.

- BDI19-18: Data loggers recorded temperatures that had dropped below the qualified temperature range for A01RC02 of -3 to 7°C between 11/8/18 and 2/15/19. There is no risk to the material, as there is no temperature specification for 6N HCl in IPA.

- BDI19-104: No temperature data was recorded for A01RC02 between 8/22/19 and 9/11/19. Prior to 8/22/19, there were multiple temperature excursions above 7.5°C. Temperatures above 7.5°C do not pose a risk to this material as there is no temperature specification for 6N HCl in IPA.

- BDI19-145: Based on temperature data, A01RC02 started to fail and lose temperature on 12/17/19. It was determined that the condenser coil needed to be replaced. Material was removed from this trailer and placed in A01RC04 and moved back to A01RC02 after it was fixed. There is no risk to the material, as there is no temperature specification for 6N HCl in IPA.

- BCC19-35: The 6N HCl in IPA normality method was updated from potentiometric titration to colorimetric titration, to align with the customer method, ensuring repeatable results of the manufactured product.

- BTOI19-67: In response to BCC19-35, a temporary operating instruction form was issued to obtain stability results for the remaining testing intervals that are representative of the initial results and previous testing intervals to ensure there is no false significant change due to the change in testing method.

- BTOI19-70: To move quality related assets from A01RC02 to A01RC04 due to the malfunctioning of A01RC02.

- BDI20-58: T_6 analysis was not performed for IH4101-005-0517 stability samples. It was likely overlooked due to the OOS assay investigation and packaging change. The material was tested from the partial drum at a pseudo T_4, and again at T_9. All results met requirements.

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6. LOT EVALUATION:

TABLE 1: RESULTS OF LONG-TERM STABILITY ANALYSES

IH4101-005-0517			
Analysis	**Appearance and Color**	**Normality**	**Identification (Chloride)**
Specification	Clear, Colorless to slightly yellow, fuming liquid	≥ 5.9N	Passes Test
T_0	Clear, colorless slightly yellowish fuming liquid	6.4N	Passes Test
T_3	Clear, colorless to slightly yellowish fuming liquid	6.0N	Passes Test
T_6	Refer to BDI20-58.		
T_9	Clear, Colorless to slightly yellow fuming liquid	6.2N	Passes Test
T_{12}	Clear, Colorless fuming liquid	6.4N	Passes Test
T_{18}	Clear, Colorless to slightly yellow fuming liquid	6.4N	Passes Test
T_{24}	Clear, slightly yellowish fuming liquid	6.3N	Passes Test
T_{36}	Clear, Colorless to slightly yellow fuming liquid	5.9N	Passes Test

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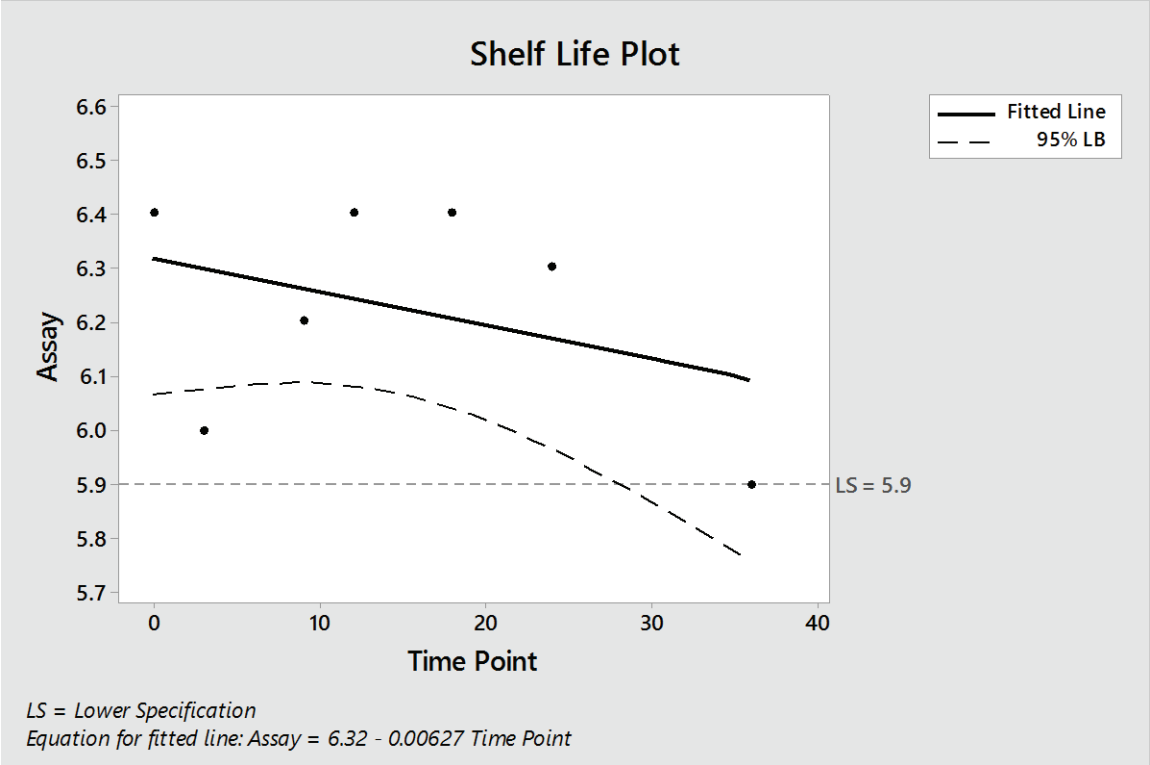
GRAPH 1: SHELF LIFE PLOT: IH4101-005-0517 ASSAY



Results for assay showed no predictable shelf life, as the mean response slope is not significantly different from zero. This is observed as there is negligible degradation of the product shown from these analyses throughout the 36 – month stability study.

7. CONCLUSION:

All data met the specifications set forth in the Stability Testing Program. In accordance with ICH Q1E 2.3.2.1, the retest date may be proposed for up to 1.5*x*, where *x* is the period covered by long- term stability data, but should be no more than 6 months beyond. The data obtained during this stability study indicated that the material packaged in 55-gallon black poly drums is stable for 36 months. A retest date of 24 months will be assigned to all 6N HCl in IPA lot manufactured at BioSpectra in the Bangor, PA facility.

8. STATEMENT OF COMMITMENT:

- BioSpectra is responsible for the following regarding Stability Data in this Report:
  - In the event that any stability analysis produces results found to be out of specification, the batch immediately before and after will be tested in full and analyzed in comparison with the batch in question.
    - This will serve to provide information to effectively ensure that the rootcause of the investigation has not impacted the batch manufactured before or after the batch in question.
  - If a stability analysis is found to be out of specification, the batch will be withdrawn from the market through communication with the Applicant and any additional

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customer. Additionally, an investigation will be conducted to determine the possible withdrawal of the batches produced before and after the batch in question.

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