BIOSPECTRA
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6N HCL IN IPA
LONG TERM STABILITY REPORT:
IH4101-006-1217-PV
IH4101-007-1217-PV
IH4101-008-0318-PV

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1. OVERVIEW:

The purpose of this report is to analyze the data obtained from the Long-Term Stability of 6N HCl in IPA manufactured at BioSpectra's Bangor, PA facility. Samples were placed on the Stability Testing Program in December 2017 and March 2018, to fulfill the requirements of adding all validation lots to the stability program. The long-term 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 Long-Term Stability analysis assesses the stability of two lots of 6N HCl in IPA that completed three years of long-term stability in December 2020 and one lot that completed three years of long-term stability in March 2021. The study included the following analyses: Appearance and Color, Assay, and Identification (Chloride). Results from all analyses are summarized in Tables 1 through 3.

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 BioSpectra to 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. BSI-ATM-0020, 6N Hydrochloric Acid in 2-Propanol (6N HCl in IPA) Testing Methods
2.2. BSI-LST-0168, 6N HCl in IPA Stability Data Card
2.3. BSI-SOP-0136, Stability Testing Program
2.4. BSI-SOP-0146, Stability Inventory
2.5. Current USP
2.6. ICH Q1

3. SAMPLE DESIGNATION:

Samples placed on the Stability Testing Program consisted of two lots of 6N HCl in IPA for the year 2017 and one lot for the year 2018. Stability samples were stored in partial drums.

4. STORAGE:

It should be noted that there is no temperature specification for the storage of this material. The 6N HCl in IPA lots were stored in A01RC02. The material was stored in Refrigerated Storage Containers which have a temperature specification of 2 - 8°C. The material was mostly stored in A01RC02, 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 A01RC02 prior to April 2018. From April 2018 through the end of the study, the temperature was monitored consistently, using temp-mate single use data loggers which record for 110 days. The minimum temperature reached in the storage container during this time was -3.7°C. The maximum temperature reached in the storage container during this time was 29.3°C. The mean temperature during this time was 4.0°C. See section 5 for investigations.

5. INVESTIGATIONS AND TEMPORARY OPERATING INSTRUCTIONS:

5.1. BLI17-66: A questionable result of 6.27N was obtained for IH4101-006-1217-PV T=0. The root cause was determined to be analyst error in determining the density of the sample, which affected the assay result. With the corrected density, the normality result was 5.9N. There was no product impact.

5.2. BLI18-15: IH4101-006-1217-PV yielded an out of specification result for assay at the T=6 time interval. The result was 5.8N with a specification of ≥5.9N. The root cause was suspected sample contamination as all retests met specification. The official result was reported as 6.0N. An extra sample at T=8 was pulled. Refer to results table.

5.3. BLI18-38: IH4101-006-1217-PV yielded an out of specification result for assay at the T=12 time interval. The result was 5.8N with a specification of ≥5.9N. The root cause of the OOS result was determined to be titrant value and all retests yielded results within specification. The official result was reported as 5.9N. There was no product impact.

5.4. 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.

5.5. BDI19-40: IH4101-008-0318-PV testing at the 12-month time point was not tested within the required timeframe of sampling due to instrument troubleshooting. Upon further investigation, it was noted that the KHP sample size was too small to obtain reliable results, so the Standardization of Titrants SOP was updated to reflect a larger sample size. The Sodium Hydroxide was successfully standardized and all samples were able to be analyzed and met specifications.

5.6. BDI19-104: New temp-mates were placed in A01RC01 and A01RC02 on 5/3/19 and were removed on 9/11/19 even though they should have been replaced on 8/22/19 due to their 110-day recording span. As a result, there was no temperature data recorded in these chambers between 8/22/19 and 9/11/19. There is no risk to the material, as there is no temperature specification for 6N HCl in IPA.

5.7. 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.

5.8. BLI19-48: IH4101-006-1217-PV yielded an out of specification assay result at the T=24 time interval. The result obtained was 5.7N with a specification of ≥5.9N. At the conclusion of the investigation, the OOS result was confirmed. BDI20-07 was initiated due to the failure.

5.9. BDI20-07: Lot IH4101-006-1217-PV at the 24-month time point yielded an out of specification normality result of 5.8N using BTOI19-67. Three replicates were performed on the resampled stability drum and the average result was 5.6N. The shelf life of lot IH4101-006-1217-PV is 2 years.

5.10. BDI20-170: Temperature monitoring was not continuous from 9/11/19 to 11/17/20 due to loggers not being replaced prior to the tempmate reaching the maximum number of readings. 7/16/20 to 7/31/20 were not temperature monitored. There is no risk to the material, as there is no temperature specification for 6N HCl in IPA.

5.11. BDI21-220: The analyst that performed normality testing on lot IH4104-008-0318-PV at the 36-month time point yielded a failing normality result of 5.8N and did not notify management nor issue a checklist. The OOS result was noted during review, upon which an investigation was initiated. The result was obtained on 3/31/21 and review was not started until 9/23/21, therefore a retest could not be performed due to the time elapsed. The shelf life of this product is 24 months.

5.12. BTOI19-67: In response to BCC19-35, a temporary operating instruction 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.

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

6. LOT EVALUATION:

TABLE 1: IH4101-006-1217-PV PARTIAL DRUM

Analysis	Appearance and Color	Assay	Identification (Chloride)
Specification	Clear, Colorless to slightly yellowish, fuming liquid	≥ 5.9N	Passes Test
T_0	Clear, Colorless to slightly yellowish fuming liquid	5.9	Passes Test
T_3	Clear, Colorless to slightly yellowish fuming liquid	5.9	Passes Test
T_6	Clear, Colorless to slightly yellowish fuming liquid	6.0	Passes Test
T_8[1]	Clear, Colorless to slightly yellowish fuming liquid	6.0	Passes Test
T_9	Clear, Colorless to slightly yellowish fuming liquid	6.0	Passes Test
T_{12}	Clear, Colorless to slightly yellowish fuming liquid	5.9	Passes Test
T_{18}	Clear, Slightly yellowish fuming liquid	5.9	Passes Test
T_{24}	Clear, Colorless to slightly yellowish fuming liquid	5.8[2]	Passes Test
T_{36}	Clear, Colorless to slightly yellowish fuming liquid	5.4	Passes Test

[1] Refer to BLI18-15.
[2] Refer to BLI19-48, BDI20-07.

TABLE 2: IH4101-007-1217-PV PARTIAL DRUM

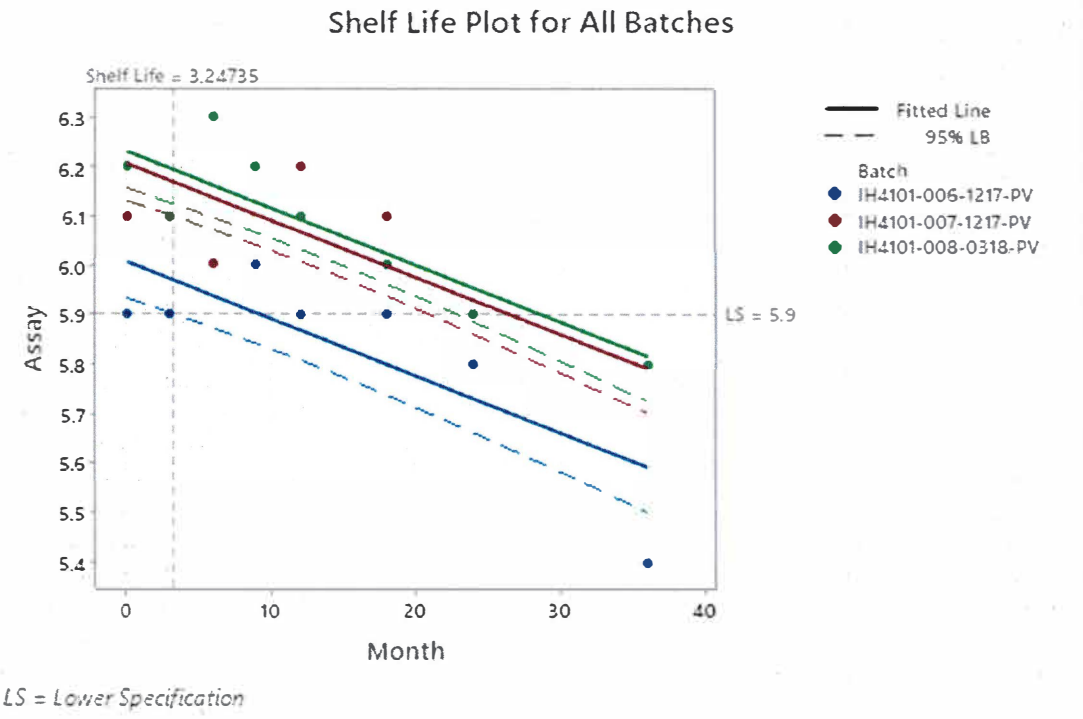
Analysis	Appearance and Color	Assay	Identification (Chloride)
Specification	Clear, Colorless to slightly yellowish, fuming liquid	≥ 5.9N	Passes Test
T_0	Clear, Colorless to slightly yellowish fuming liquid	6.1	Passes Test
T_3	Clear, Colorless to slightly yellowish fuming liquid	6.1	Passes Test
T_6	Clear, Colorless to slightly yellowish fuming liquid	6.0	Passes Test
T_9	Clear, Colorless to slightly yellowish fuming liquid	6.2	Passes Test
T_{12}	Clear, Colorless to slightly yellowish fuming liquid	6.2	Passes Test
T_{18}	Clear, Colorless to slightly yellowish fuming liquid	6.1	Passes Test
T_{24}	Clear, Colorless to slightly yellow fuming liquid	5.9	Passes Test
T_{36}	Clear, Colorless to slightly yellow fuming liquid	5.8[1]	Passes Test

[1]Shelf life is 24 months.

TABLE 3: IH4101-008-0318-PV

Analysis	Appearance and Color	Assay	Identification (Chloride)
Specification	Clear, Colorless to slightly yellowish, fuming liquid	≥ 5.9N	Passes Test
T_0	Clear, Colorless to slightly yellowish fuming liquid	6.2	Passes Test
T_3	Clear, Colorless to slightly yellowish fuming liquid	6.1	Passes Test
T_6	Clear, Colorless to slightly yellowish fuming liquid	6.3	Passes Test
T_9	Clear, Colorless to slightly yellowish fuming liquid	6.2	Passes Test
T_{12}	Clear, Colorless to slightly yellowish fuming liquid	6.1	Passes Test
T_{18}	Clear, Colorless to slightly yellowish fuming liquid	6.0	Passes Test
T_{24}	Clear, Colorless to slightly yellow fuming liquid	5.9	Passes Test
T_{36}	Clear, Colorless fuming liquid	5.8[1]	Passes Test

[1]Refer to BDI21-220, shelf life is 24 months.



LS = Lower Specification

GRAPH 1: SHELF LIFE PLOT: ASSAY

Results for assay showed a shelf life of 3.24735 months using the 95% confidence level.

7. CONCLUSION:

In accordance with ICH Q1E, 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. While the Shelf life plot for assay resulted in a shelf life of 3 months, the data obtained during this stability study indicated that the material packaged in 55-gallon black poly drums is stable for 24 months. However, one of the three lots did not meet the T=24. These batches were made prior to preventative actions established in BDI20-07, including the tightening of in process specifications, revision to testing methods and storage of stability samples. The shelf life will continuously be evaluated through the stability testing program. 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:

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

8.1.1. In the even 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.

8.1.1.1. 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.

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

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