BIOSPECTRA
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WATER FOR INJECTION 2023
REAL-TIME STABILITY REPORT

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1. OVERVIEW:

The purpose of this report is to analyze and conclude on the data obtained from the real-time stability study of Water for Injection (WFI). 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 confirm that the manufactured product remains stable under the specified conditions and 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 real time stability analysis will assess the stability of Water for Injection, lot L08DI01-022223, that completed nine months of real-time stability in November 2023. The study included the following analyses: Endotoxin, Conductivity, Microbial, Nitrates, Oxidizable Substances, Total Organic Carbon (TOC) and Appearance. 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 Water for Injection.

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 consisted of one lot of Water for Injection. Stability samples from this batch were put into a TepoFlex Sample Bag packaging configuration. The samples were packaged in accordance with Stability Inventory, DCN: BSI-SOP-0146. Reference Table 1, below, for the packaging configuration and description. The type of packaging utilized in this stability study was based on BioSpectra's packaging offered.

TABLE 1: PACKAGING DETAILS

Packaging Configuration	Packaging Description
TepoFlex Sample Bag	TepoFlex 1L Polyethylene bio-containers premade one time use bags designed specifically for fluid handling

4. STORAGE:

4.1. For this study, the Water for Injection lot was stored at room temperature in a well closed container. The samples were placed in the Real Time Stability Chamber at the Bangor, PA facility from February 2023 until November 2023. Storage conditions have been continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature (25 ± 2°C) and humidity (60%RH ±5%RH). For this period, the maximum temperature recorded was 25.69°C, the minimum temperature was 25.07°C, the average temperature was 25.42°C, and the Average Mean Kinetic Temperature was 25.42°C. The average humidity for this period was 62.0%. Section 5 will include any excursions from these conditions that resulted in an investigation.

5. INVESTIGATIONS:

5.1. No investigations have been issued to date.

6. LOT EVALUATION:

TABLE 2: WATER FOR INJECTION LOT L08DI01-022223 TEPOFLEX SAMPLE BAG

Analysis	Specification	T_0	T_3	T_6	T_9
Endotoxin	<0.25 EU/mL	<0.0100 EU/mL	<0.0100 EU/mL	<0.0100 EU/mL	<0.0100 EU/mL
Conductivity	[1]QC Online Meter	0.72 @ 23.4°C	Not Applicable	Not Applicable	Not Applicable
Microbial	<10 CFU/100 mL	<1 CFU/100 mL	<1 CFU/100 mL	<1 CFU/100 mL	<1 CFU/100 mL
Nitrates	0.2 ppm maximum	<0.2 ppm	<0.2 ppm	<0.2 ppm	<0.2 ppm
Oxidizable Substances	Pass Test	Pass Test	Pass Test	Pass Test	Pass Test
TOC	[1]QC Online Meter	1.41 ppb	Not Applicable	Not Applicable	Not Applicable
Appearance	Clear/Colorless Liquid	Clear/Colorless Liquid	Clear/Colorless Liquid	Clear/Colorless Liquid	Clear/Colorless Liquid

[1]Results for T=0 for Conductivity and TOC were recorded from online meters at the time of packaging, and stand as the official result. Manual testing for Conductivity, Oxidizable Substances, and TOC will continue throughout the study, but will be for information only (FOI).

- Future Pulls:
  - T=12: Scheduled for 02/23/24
  - T=18: Scheduled for 08/23/24
  - T=24: Scheduled for 02/23/25
  - T=36: Scheduled for 02/23/26

7. CONCLUSION:

All data met the specification set forth in the Stability Testing Program for the Water for Injection lot L08D101-022223 when packaged in TepoFlex Sample Bag packaging. In accordance with ICH Q1E, the retest date may be proposed for up to 2*x*, where *x* is the period covered by long-term stability data, but should be no more than 12 months beyond. The data obtained during this stability study indicates that Water for Injection packaged in TepoFlex Sample Bag packaging is stable for 18 months.

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 real time 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 and the product has an established shelf life, the batch will be withdrawn from the market through communication with any 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.