# URACIL 2018
# LONG TERM STABILITY REPORT

## TABLE OF CONTENTS

## 1. OVERVIEW:

The purpose of this Report is to assess and conclude on the data obtained from the Long-Term Stability Study of Uracil manufactured at the Bangor, PA facility. The 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 declare 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 period for the finished good product.

The data can be found in the Uracil Real Time Stability Program binders. This Long-Term Stability report assesses the stability of three Process Validation lots of Uracil Bio Excipient Grade. The lots were placed on stability in 2015, concluding the stability studies in 2018. The Uracil Stability samples were placed on stability one month after manufacturing. Therefore, this study includes one additional testing interval at 35 months; stability samples were analyzed as this was 36 months from the date of manufacturing.

The stability indicating analyses for Uracil are Appearance and Color, Identification (IR), Reaction and Solubility, and Loss on Drying which was added to the Uracil Stability Analysis Sheet DCN 17-002152 v.2.0 effective 7/13/18. Loss on Drying was added at the discretion of the Quality Control Manger as a Monitor. Loss on Drying was only analyzed at testing intervals $T_{35}$ and $T_{36}$. There will be no Shelf Life plots utilized to analyze the data for Uracil as Loss on Drying is the only analysis that yields quantitative results and there are too few data points for it to be analyzed. The results obtained from the Uracil Long Term Stability Study are be reported in Table 1 and Table 2 below.

## 2. SAMPLE DESIGNATION:

Samples initially placed on the Stability Testing Program consisted of all process validation batches manufactured in 2015. Stability samples from each of these batches were packaged in a poly pail with a poly liner representative of Finished Goods packaging. Samples were placed in the Long Term Stability area located in the Stroudsburg, PA BioSpectra facility

## 3. STORAGE:

Although there are no storage conditions for Uracil, storage conditions have been continuously measured and recorded utilizing MadgeTech data loggers with regulated conditions for temperature (15-30°C) and humidity (monitor).

## 4. STABILITY DATA:

**Table 1. Appearance and Color, Identification (IR), Reaction and Solubility**

| ANALYSIS | SPECIFICATION | TIME POINT | UC4201-001-0915-PV | UC4201-002-0915-PV | UC4201-003-0915-PV |
|---|---|---|---|---|---|
| APPEARANCE AND COLOR | WHITE TO SLIGHTLY YELLOW POWDER | $T_0$ | White to Slightly Yellow Powder | White to Slightly Yellow Powder | White to Slightly Yellow Powder |
| | | $T_3$ | White to Slightly Yellow Powder | White to Slightly Yellow Powder | White to Slightly Yellow Powder |
| | | $T_6$ | White to Slightly Yellow Powder | White to Slightly Yellow Powder | White to Slightly Yellow Powder |
| | | $T_9$ | White to Slightly Yellow Powder | White to Slightly Yellow Powder | White to Slightly Yellow Powder |
| | | $T_{12}$ | White to Slightly Yellow Powder | White to Slightly Yellow Powder | White to Slightly Yellow Powder |
| | | $T_{18}$ | White to Slightly Yellow Powder | White to Slightly Yellow Powder | White to Slightly Yellow Powder |
| | | $T_{24}$ | White to Slightly Yellow Powder | White to Slightly Yellow Powder | White to Slightly Yellow Powder |
| | | $T_{35}$ | White to Slightly Yellow Powder | White to Slightly Yellow Powder | White to Slightly Yellow Powder |
| | | $T_{36}$ | White to Slightly Yellow Powder | White to Slightly Yellow Powder | White to Slightly Yellow Powder |
| IDENTIFICATION (IR) | PASSES TEST | $T_0$ | Passes Test | Passes Test | Passes Test |
| | | $T_3$ | Passes Test | Passes Test | Passes Test |
| | | $T_6$ | Passes Test | Passes Test | Passes Test |
| | | $T_9$ | Passes Test | Passes Test | Passes Test |
| | | $T_{12}$ | Passes Test | Passes Test | Passes Test |
| | | $T_{18}$ | Passes Test | Passes Test | Passes Test |
| | | $T_{24}$ | Passes Test | Passes Test | Passes Test |
| | | $T_{35}$ | Passes Test | Passes Test | Passes Test |
| | | $T_{36}$ | Passes Test | Passes Test | Passes Test |
| REACTION | PASSES TEST | $T_0$ | Passes Test | Passes Test | Passes Test |
| | | $T_3$ | Passes Test | Passes Test | Passes Test |
| | | $T_6$ | Passes Test | Passes Test | Passes Test |
| | | $T_9$ | Passes Test | Passes Test | Passes Test |
| | | $T_{12}$ | Passes Test | Passes Test | Passes Test |
| | | $T_{18}$ | Passes Test | Passes Test | Passes Test |
| | | $T_{24}$ | Passes Test | Passes Test | Passes Test |
| | | $T_{35}$ | Passes Test | Passes Test | Passes Test |
| | | $T_{36}$ | Passes Test | Passes Test | Passes Test |

| ANALYSIS | SPECIFICATION | TIME POINT | UC4201-001-0915-PV | UC4201-002-0915-PV | UC4201-003-0915-PV |
|---|---|---|---|---|---|
| SOLUBILITY | PASSES TEST | $T_0$ | Passes Test | Passes Test | Passes Test |
| | | $T_3$ | Passes Test | Passes Test | Passes Test |
| | | $T_6$ | Passes Test | Passes Test | Passes Test |
| | | $T_9$ | Passes Test | Passes Test | Passes Test |
| | | $T_{12}$ | Passes Test | Passes Test | Passes Test |
| | | $T_{18}$ | Passes Test | Passes Test | Passes Test |
| | | $T_{24}$ | Passes Test | Passes Test | Passes Test |
| | | $T_{35}$ | Passes Test | Passes Test | Passes Test |
| | | $T_{36}$ | Passes Test | Passes Test | Passes Test |

**Table 2. Loss on Drying**

| ANALYSIS | SPECIFICATION | TIME POINT | UC4201-001-0915-PV | UC4201-002-0915-PV | UC4201-003-0915-PV |
|---|---|---|---|---|---|
| LOSS ON DRYING | MONITOR | $T_{35}$ | 0.0500% | 0.0720% | 0.1475% |
| | | $T_{36}$ | 0.0500% | 0.1099% | 0.0900% |

## 5. CONCLUSION:

Long Term Stability Data obtained for lots manufactured in 2015 indicate that the material packaged in a poly pail with a poly liner is stable for of 36 months. A 36 month expiration date will be set for all Finished Good lots packaged in poly pails with a poly liner since all lots that have reached the 36 month data point have met specifications.

## 6. 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 produced 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 root cause 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 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.

# URACIL
# REAL-TIME STABILITY REPORT:
# UC4201-006-0317

## TABLE OF CONTENTS

## 1 OVERVIEW:

The purpose of this report is to analyze the data obtained from the Real-Time Stability of Uracil manufactured at BioSpectra's Bangor, PA facility. Samples were placed on the Stability Testing Program in March 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 Uracil that completed three years of long-term stability in March 2020. The study included the following analyses: Appearance and Color, Identification (IR), Reaction, and Solubility. Loss on Drying was added to the study in September 2018, at $T_{18}$. Results from all analyses are summarized in Table 1.

## 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 Uracil. Stability samples were individually placed into small poly bags and were sealed with a ziptie. All small poly bags were then placed into one larger poly bag and sealed with a ziptie. The large poly bag containing all samples was then placed into a poly pail and sealed. This packaging configuration is denoted as 2Poly/Poly (2P/P). The type of packaging utilized in this stability study was based on BioSpectra packaging offered to the customer.

## 4 STORAGE:

At the start of this stability study, Uracil stability samples were being stored in the Zone M Warehouse. Due to the inability to control the temperature of the warehouse during the summer months, the stability samples were relocated to the Long-term stability chamber.

From March 24, 2017 through September 25, 2019, the samples were stored in the Zone M Warehouse. The temperature was monitored continuously using MadgeTech data loggers. The maximum temperature of the warehouse during the stability study was 33.67°C and the minimum temperature of the warehouse was 12.20°C (refer to BDI18-20).

On September 25, 2019, all stability samples were moved from the Zone M Warehouse to the Long-term stability chamber. The samples were stored in this location until the end of the 36-month stability study on March 22, 2020. The temperature was monitored continuously using MadgeTech data loggers, with an allowable temperature range of 23°C – 27°C. The minimum temperature reached during this time was 23.97°C and the maximum temperature reached was 25.71°C.

## 5 INVESTIGATIONS:

5.1 BDI18-20: The temperature Alarm Notifications were not received by BioSpectra due to the way the alarms rules were established. The temperature in the Zone M Warehouse was reported as less than 15°C on multiple dates ranging from 12/28/17 to 3/4/18. The average temperature was reported as 18.87°C and the minimum temperature was reported as 12.20°C. $T_9$ and $T_{12}$ samples were pulled and tested during this timeframe, and all results met specification.

## 6 LOT EVALUATION:

**TABLE 1: RESULTS OF LONG-TERM STABILITY ANALYSES**

| UC4201-006-0317 | | | | | |
|---|---|---|---|---|---|
| **Analysis** | **Appearance and Color** | **Identification (IR)** | **Loss on Drying** | **Reaction** | **Solubility** |
| Specification | White to Slightly Yellow Powder | Passes Test | Monitor | Passes Test | Passes Test |
| $T_0$ | White to Slightly Yellow Powder | Passes Test | N/A | Passes Test | Passes Test |
| $T_3$ | White to Slightly Yellow Powder | Passes Test | N/A | Passes Test | Passes Test |
| $T_6$ | White to Slightly Yellow Powder | Passes Test | N/A | Passes Test | Passes Test |
| $T_9$ | White to Slightly Yellow Powder | Passes Test | N/A | Passes Test | Passes Test |
| $T_{12}$ | White Powder | Passes Test | N/A | Passes Test | Passes Test |
| $T_{18}$ | White to Slightly Yellow Powder | Passes Test | 0.0819% | Passes Test | Passes Test |
| $T_{24}$ | White to Slightly Yellow Powder | Passes Test | 0.0697% | Passes Test | Passes Test |
| $T_{36}$ | White to Slightly Yellow Powder | Passes Test | 0.0902% | Passes Test | Passes Test |

## 7 CONCLUSION:

All data met the specifications set forth in the Stability Testing Program. In accordance with ICH Q1E 2.4.2.1, 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 the material packaged in 2P/P packaging is stable for 36 months. A retest date of 36 months will be assigned to all Uracil lots 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 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.

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