BIOSPECTRA
100 Majestic Way, Bangor, PA 18013 / www.biospectra.us

VALIDATION EXTERNAL REPORT

VALIDATION REPORT FOR THE MANUFACTURE OF:

Uracil

TO BE MANUFACTURED AS THE FOLLOWING CODES:

URAC-4202

TO BE MANUFACTURED AT:

BIOSPECTRA, INC., 100 MAJESTIC WAY BANGOR, PENNSYLVANIA, 18013

IN COMPLIANCE WITH THE STANDARDS OF:

IPEC / PQG JOINT GOOD MANUFACTURING PRACTICE GUIDE

MANUFACTURED TO BE SUITABLE FOR USE AS

GMP PROCESS CHEMICAL

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1. INTRODUCTION

The Validation of a manufacturing process used to produce process chemicals is a requirement under IPEC-PQG Joint Good Manufacturing Practice Guide. The objective of this validation study was to assure that the manufacturing process in Zone E for Uracil, product code, URAC-4202, is a controlled and validated process capable of consistently producing material that meets pre-established specifications and critical quality attributes. This validation study was conducted due to the following change controls, BCC21-78, initiated because the current 0.8-micron polishing filter has been replaced with a new approved 0.8-micron filter. BCC21-82, initiated to increase the manufacturing capacity by utilizing additional Process Rooms (E04 Wet Process/E06 Separation Process or E05) in Zone E of the Bangor, PA facility, there is no change in scale of the current process. Notification DCN: NOTIF21-469 was sent to provide notification of these changes. The implementation date of these changes was 9/28/21.

This external validation report for Uracil Validation Study will summarize the validation study results for the first validation batch manufactured after the issuance of the validation protocol. This validation study was performed to ensure that the Uracil process conforms to the pre-established critical process parameters established in previous validation studies. This validation was a concurrent validation study allowing for the release of the validation batch for commercial distribution based on approval of the executed batch record and documented evidence that the batch conforms to the finished goods specifications before release.

2. OBJECTIVE

The objective of this external Validation Report is to verify and assure that the manufacturing process for Uracil consistently produces material that meets a set of pre-determined specifications as listed in Table I.

Batch one of the Uracil Validation was manufactured according to the current revision of the Batch Record. Once the manufacture of the batch was completed, representative samples were submitted to the QC Laboratory and were tested against Finished Good specifications. This was conducted to verify that the process is capable of consistently producing material that meets Finished Good Specifications.

3. SCOPE

This Report applies to the manufacturing process for Uracil, Bio Pharma Grade which includes the following process steps: charging the raw materials, mixing and heating, recirculating, filtering/purification, cooling to crystallize, separation and washing of crystal from mother liquor by centrifuge or funnel filter (for the purpose of this validation the funnel filter was utilized), drying, packaging, and the testing of the finished product.

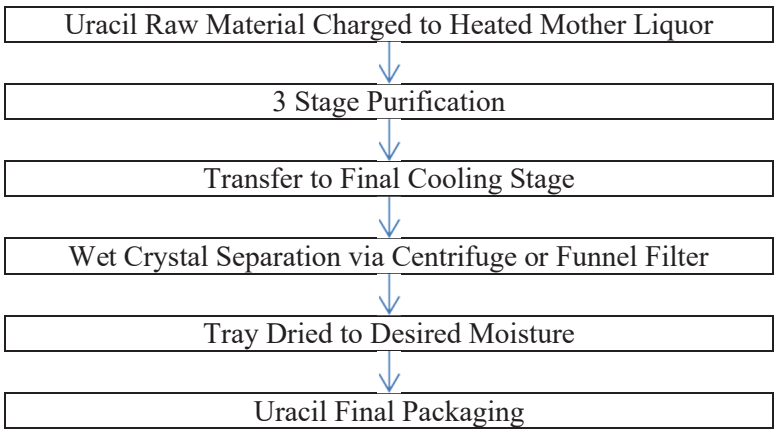
Specifications and approval requirements for all Raw Materials (RM) and components have been created; therefore, these RM and components approval are not covered by this Report except that only approved RM and components were used.

4. EXECUTIVE SUMMARY

The Uracil manufacturing process is a manufacturing/purification process with Critical Process Parameters as detailed in the Validation Protocol. The CPP's were developed during the original validation study were found to be in accordance with BioSpectra's Manufacturing Process Validation Master Plan. The utilities and process used in the manufacture of this product have been qualified in accordance with BioSpectra's Equipment Qualification Master Plan. The equipment for manufacturing in process rooms (E04/E06, E05) are like for like to the previously validated process rooms (E02/E03). This validation was for Process Rooms E04WP01/E06SP01 only, the validation for Process Room E05 is pending execution. The Process consists of the creation of a Uracil solution Mother Liquor, using approved raw material Sodium Hydroxide, Purified Water, and Uracil and adding them to the Hot Tank, heated by the Zone E Boiler. Once the Uracil Raw Material is in solution, now called mother liquor (ML), it is recirculated to begin filtration. It circulates through the Cartridge Filter, Zeta Filters, Polishing Filter, and back to the Hot Tank for the time specified in the Batch Record. After purification and cooling, the ML is then transferred to the centrifuge or funnel filter, and the wet crystal is collected on the filter cloth and washed with Purified Water. The ML is drawn through the centrifuge or funnel filter via vacuum pressure from the vacuum system and returned back to the Hot Tank via the Diaphragm Pump. The washed wet crystals are loaded on to dedicated HDPE trays and stacked in the Drying Room where operators use product dedicated mortar and pestles to crush the material into a fine powder. Finally, once the product has met in process specifications, it is sampled and tested against finished goods specifications and packaged for release.

5. PROCESS FLOW DIAGRAM

URACIL BIO PHARMA GRADE
PROCESS FLOW DIAGRAM



6. ANALYSIS

The first Uracil validation batch was manufactured in accordance with the current Uracil Bio Pharma Grade Batch Record DCN: BSI-MPR-0050, has met the BioSpectra analytical requirements associated with product code URAC-4202. The results can be found in Table 1. All in-process and Finished Goods analyses were met as required in the Validation study and for finished good release.

TABLE 1: Critical Quality Attributes Results from Previous Validation and Current Validation

CQA Analysis	CQA/ Specification	2020 Validation	2021 Validation
		UC4200-017-0320-PV	URAC-0121-00021-PV
		Manufactured 3/31/20	Manufactured 9/28/21
Appearance and Color	**White To Slightly Yellow Powder**	White to Slightly Yellow Powder	White Powder
Assay (Acid Titration)	**97.0-102.0%**	97.6%	98.6%
Identification (IR)	**Passes Test**	Passes Test	Passes Test
Reaction	**Passes Test**	Passes Test	Passes Test
Solubility	**Passes Test**	Passes Test	Passes Test

7. ADDITIONAL INFORMATION

7.1. Degradation and Impurity Profile: BSI-PRL-0148

7.1.1. A Degradation and Impurity profile was initiated for this validation and includes an assessment of the raw material, in process and finished goods analysis for Appearance and Color, Assay, Identification Test (IR), Loss on Drying, pH of a 1% Solution or Slurry @ 25 ± 2°C, Total Alkali as Sodium Hydroxide, and Trace Metals.

7.2. Stability Study: BSI-LST-0154

7.2.1. In accordance with BioSpectra's Stability Testing Program all validation / revalidation batches must be added to the stability program. The Stability Analysis for Uracil consists of an evaluation of the following analyses listed in Table 2. These analyses were selected based on a combination of incoming raw material specifications, finished goods requirements and known process information and the specifications were set based on this same information. Table 2 indicates which analyses are required for the Stability testing of Uracil at intervals 0, 3, 6, 9, 12, 18, 24, 36, 48, and 60-month intervals.

TABLE 2: STABILITY ANALYSIS

Analysis
Appearance and Color
Assay
Identification (IR)
Loss on Drying
Reaction
Solubility

8. CONCLUSION

BioSpectra has manufactured one batch of validated Uracil, Bio Pharma Grade, to be compliant with key compliance grades up to and including the Bio Pharma grade. This Bio Pharma Grade classification requires that a product be manufactured in accordance with IPEC guidelines to be suitable for use as a GMP manufactured process chemical. The results obtained in this validation report deem Uracil manufactured using this process and analyzed to URAC-4202 acceptable. The utilities and process used in the manufacture of this product have been qualified in accordance with BioSpectra's Equipment Qualification Master Plan. The results reported from the Validation Study for Uracil have provided the evidence necessary to state that the approved change, using a new filter supply has not impacted the quality and physical characteristics of Uracil for product code URAC-4202. All Raw Materials used for the processing of Uracil were approved before use in accordance with RM specifications. The Validation samples of Uracil will be placed into Real Time Stability and will be reported on annually. The Stability Study does not impact the current re-test date or previous stability studies. All Finished Goods samples analyzed for batch one of this validation study met Finished

Good Specifications for URAC-4202. The change in process rooms and filter is considered acceptable causing no impact to the quality, impurity and physical characteristics of Uracil. The first batch produced after the implementation of the changes detailed in this validation report was URAC-0121-00025.