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

BioSpectra Validation Report

Revalidation Protocol for the Manufacture of:

HEPES; 4-(2-Hydroxyethyl) Piperazine-1-Ethanesulfonic Acid

To be Manufactured as the Following Codes:

HEPES

HEPE-3200 or Below Compliance Grade

To be Manufactured at:

BioSpectra, Inc., 100 Majestic Way, Bangor Pennsylvania, 18013

In Compliance with the Standards of:

The Joint IPEC – PQG Good Manufacturing Practice Guide

ICH Q7 Good Manufacturing Practice Guide

Manufactured to be Suitable for Use as:

An Excipient

TABLE OF CONTENTS

1. INTRODUCTION:

The Validation of a manufacturing process used to produce excipients is a requirement under IPEC and ICH Q7 guidelines. The objective of this validation study was to assure that the manufacturing process in Process Room E02 or E03 in Zone E at BioSpectra's Bangor, PA facility for product codes, HEPE-3220, HEPE-3221 and HEPE-3250, is a controlled and validated process capable of consistently producing material that meets pre-established specifications and critical quality attributes. This re-validation study is for replacing the currently validated 10" 0.8-micron cartridge filter, with a 10" 0.8-micron cartridge filter, from a different filter supply, in the HEPES manufacturing process located in Zone E of BioSpectra's Bangor, PA Facility, the change may be referenced as BCC21-78. The validation seeks to prove that the HEPES manufacturing process in Process Room E02 or E03 is capable of consistently delivering quality product when manufactured using the new filter supply.

This HEPES validation Study consisted of three concurrent validation batches to ensure that the HEPES manufacturing process conforms to the pre-established critical process parameters defined prior to executing this validation protocol using tools such as process mapping, Failure Modes Effect Analysis and Cause & Effect (FMEA and C&E. A concurrent validation requires that all finished good analysis be completed and approved before each validation lot is approved for commercial distribution.

2. OBJECTIVE:

The objective of this Validation Report is to verify and assure that the manufacturing process for HEPES in Process Room E02 or E03 in Zone E at BioSpectra's Bangor, PA facility consistently produces material that meets a set of pre-determined specifications as listed in Table 1 and quality attributes.

The Validation batches of HEPES were manufactured according to the current version of the Batch Record. Once the manufacture of the batches 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 HEPES, Bio Excipient Grade which includes the following process steps: mother liquor creation or verification, raw material charge, 3 stage purification, recrystallization, wet crystal separation, tray 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 are not covered by this Report except that only approved RM and components were used.

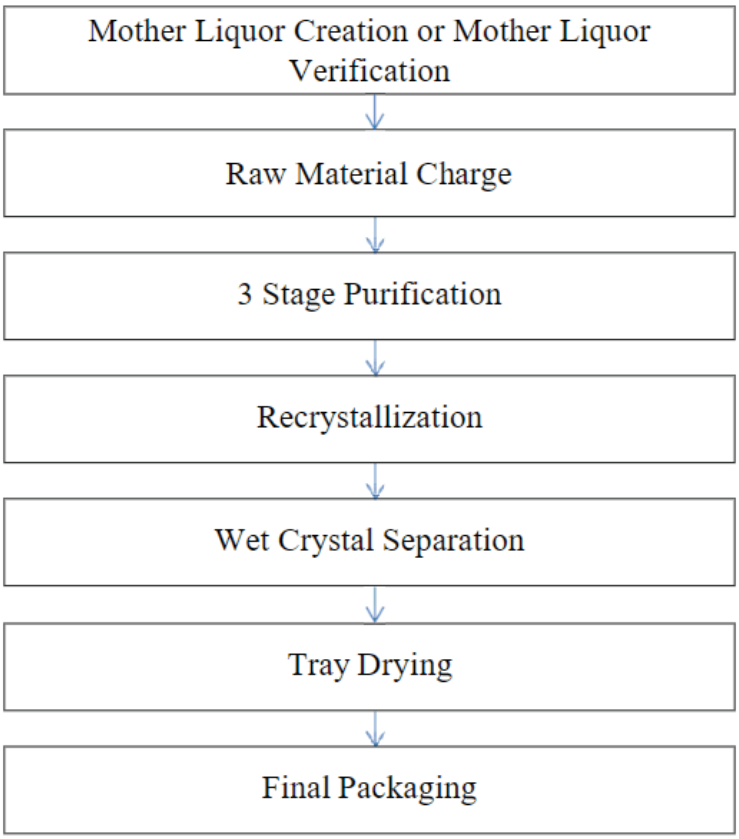
4. EXECUTIVE SUMMARY:

The HEPES manufacturing process is a manufacturing process with Critical Process Parameters as detailed in the Validation Protocol. The CPP's that were developed prior to the 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 parameters for the CPP's were varied for the validation batches to establish proven acceptable ranges for each CPP. The three validation batches manufactured for this Validation were manufactured following the current HEPES Batch Record and CPP parameter values detailed in the Validation Protocol. The manufacturing process for HEPES consistently produces material that meets a set of pre-determined specifications and attributes, passing batch uniformity and Finished Good specification testing.

5. PROCESS FLOW DIAGRAM:

HEPES Bio Excipient Manufacturing Process

(Process Room E02 or E03)



6. ANALYSIS:

The HEPES batches that were manufactured in accordance with the current HEPES Bio Excipient Grade Batch Record have met the BioSpectra analytical requirements associated with product code(s) for commercial distribution. The analytical results for the critical quality attributes (CQA) of the three validation batches 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

CQA	CQA/ Analysis		Specification	HEPE-0122-00036-PV	HEPE-0122-00037-PV	HEPE-0122-00038-PV
Purity	Absorbance (0.1M)	250 nm	0.0500 a.u. maximum	0.0059	0.0068	0.0122
		260 nm	0.0500 a.u. maximum	0.0016	0.0023	0.0073
		280 nm	0.0800 a.u. maximum	0.0010	0.0017	0.0062
	Appearance and Color		White / Crystals	White/Crystals	White/Crystals	White/Crystals
	Assay, Dried Basis		99.5% minimum	100.3%	100.6%	100.9%
	pH (5% Solution)		5.0-6.5	5.3	5.3	5.3
	pKa		7.45-7.65	7.52	7.50	7.52
Identification	Identification (IR)		Passes Test	Passes Test	Passes Test	Passes Test
Moisture	Loss on Drying		0.5% maximum	0.1%	0.1%	0.1%

7. ADDITIONAL INFORMATION:

7.1. Degradation and Impurity Profile

7.1.1. A Degradation and Impurity profile was initiated and was concurrently executed for this validation in accordance with the Degradation and Impurity Profile Protocol: HEPES Zone E DCN: BSI-PRL-0558.

7.2. Stability Study

7.2.1. The Stability Analysis for HEPES consists of an evaluation of the following analyses and associated specifications listed in Table 2 below. These analyses were selected based on a combination of incoming raw material specifications, finished good requirements and known process information and the specifications were set based on this same information. Each batch placed on the Long-Term Stability Program will undergo stability analyses at intervals 0, 3, 6, 9, 12, 18, 24, 36, 48, and 60 month intervals.

TABLE 2: Stability Analysis

Analysis		Specifications
Absorbance (0.1M)	280 nm	0.080 a.u. max
	260 nm	0.050 a.u. max
	250 nm	0.050 a.u. max
Appearance and Color		White/Crystals
Assay, Dried Basis		99.0% minimum
pH (5% Solution)		5.0-6.5
Loss on Drying		0.5% max

8. CONCLUSION:

BioSpectra has successfully manufactured three batches of HEPES, Bio Excipient Grade, to be compliant with key compliance grades up to and including the Bio Excipient Grade. This Bio Excipient Grade classification requires that a product be manufactured in accordance with ICH Q7 Good Manufacturing guidelines and is suitable for use as an excipient. The results reported in this validation report deem HEPES manufactured using this process and analyzed to finished goods specifications acceptable. The utilities and process equipment used in the manufacture of this product have been qualified in accordance with BioSpectra's Equipment Qualification Master Plan. All Raw Materials used for the processing of HEPES were approved before use in accordance with RM specifications. The Validation samples of HEPES have been placed into Real Time Stability and will be reported on annually.