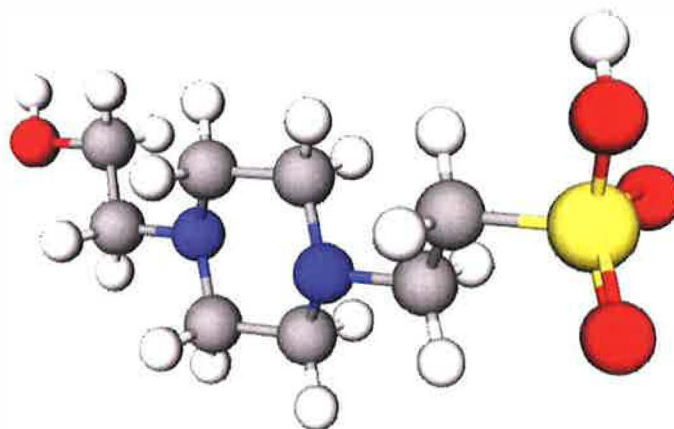




HEPES



BIO EXCIPIENT GRADE REGULATORY PACKET

Signature/Date:



TABLE OF CONTENTS

1. HEPES, BIO EXCIPIENT GRADE.....3

 1.1. GENERAL PRODUCT INFORMATION:3

 1.2. MANUFACTURING, PACKAGING, RELEASE SITE, AND SUPPLIER INFORMATION:3

 1.3. PHYSICO-CHEMICAL INFORMATION:4

 1.4. REGULATORY INFORMATION:.....8

 1.5. MISCELLANEOUS PRODUCT INFORMATION:.....10

 1.6. CONTACT INFORMATION:.....11



1. HEPES, BIO EXCIPIENT GRADE

1.1. General Product Information:

- 1.1.1. Product Name:
 - 1.1.1.1. HEPES
- 1.1.2. Product Code:
 - 1.1.2.1. Historic Code: HE3220, HE3221, HE3251
 - 1.1.2.2. Current Code: HEPE-3220, HEPE-3221, HEPE-3251
- 1.1.3. Scope:
 - 1.1.3.1. This regulatory packet will provide the quality and regulatory information regarding the manufacturing, testing, packaging, storage, release, shipping and handling of Bio Excipient Grade HEPES manufactured by and at the BioSpectra, Bangor, PA facility and the BioSpectra, Stroudsburg, PA facility.
- 1.1.4. Molecular Formula:
 - 1.1.4.1. $C_8H_{18}N_2O_4S$
- 1.1.5. Molecular Weight:
 - 1.1.5.1. 238.30 g/mol

1.2. Manufacturing, Packaging, Release Site, and Supplier Information:

- 1.2.1. General Information:
 - 1.2.1.1. BioSpectra manufactures HEPES in its Bangor, PA facility and Stroudsburg, PA facility. HEPES is manufactured, packaged, stored, tested and released at BioSpectra's Bangor, PA and Stroudsburg, PA facility.
 - 1.2.1.2. HEPES is additionally stored and shipped at BioSpectra's Supply Chain Center: 51 North 3rd Street, Stroudsburg, PA 18360.
- 1.2.2. Manufacturing:
 - 1.2.2.1. The manufacturing of HEPES is performed at BioSpectra's Bangor, PA facility and Stroudsburg, PA facility utilizing multiuse equipment. Equipment used in the manufacturing of HEPES is cleaned in accordance with BioSpectra's Cleaning Worksheet Procedure.
- 1.2.3. Packaging:
 - 1.2.3.1. The packaging of HEPES occurs in the following BioSpectra sites: BioSpectra Bangor, PA Facility: 100 Majestic Way, Bangor, PA 18013, and BioSpectra Stroudsburg, PA Facility: 1474 Rockdale Lane, Stroudsburg, PA 18360
- 1.2.4. Testing for Release:
 - 1.2.4.1. Testing and release of HEPES is performed at: BioSpectra Bangor, PA Facility: 100 Majestic Way, Bangor, PA 18013, and BioSpectra Stroudsburg, PA Facility: 1474 Rockdale Lane, Stroudsburg, PA 18360
- 1.2.5. GMP Compliance Statement:
 - 1.2.5.1. Bio Excipient Grade HEPES is suitable for use as an excipient. It is manufactured in accordance with the ICH Q7 Good Manufacturing Practice Guide. This Grade of HEPES is not suitable to be used as an Active Pharmaceutical Ingredient, Drug Product or Household Item.

**1.3. Physico-Chemical Information:**

1.3.1. CAS Number:

1.3.1.1. CAS# 7365-45-9

1.3.2. Origin:

1.3.2.1. The origin of HEPES is through chemical manufacturing using approved raw materials, which are further purified in accordance with ICH Q7 guidelines. Raw materials of synthetic origin are used in the synthesis and purification of HEPES.

1.3.3. Synonyms:

1.3.3.1. N-(2-Hydroxyethyl) Piperazine-N'-2-Ethanesulfonic Acid

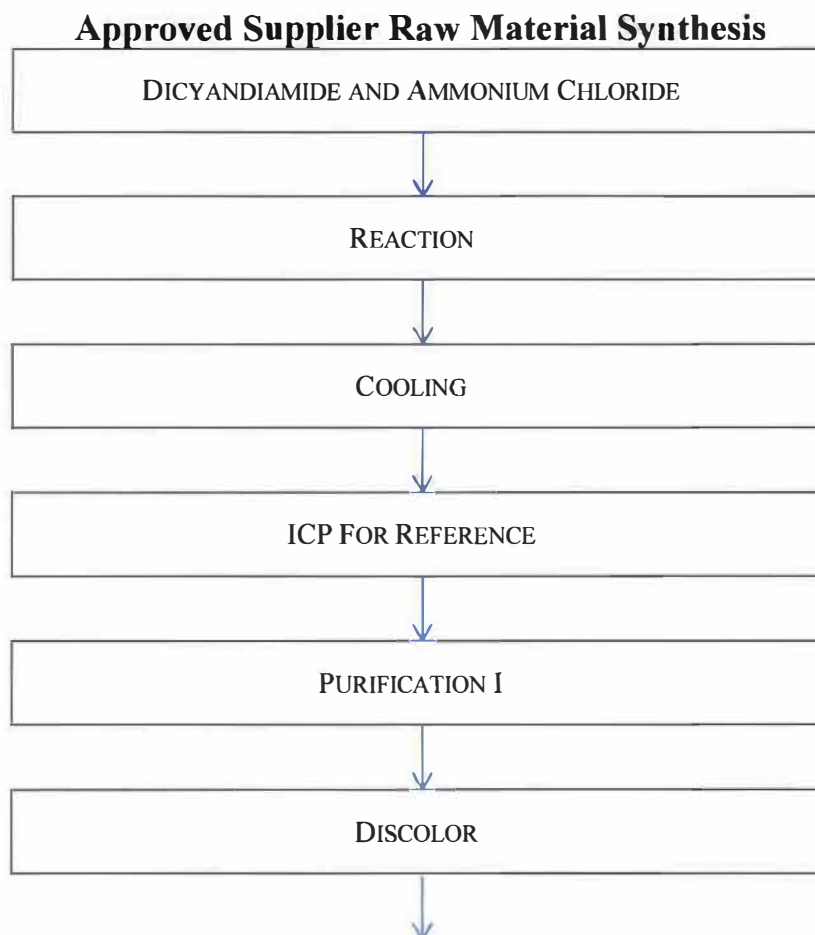
1.3.3.2. 4-(2-Hydroxyethyl) Piperazine-1-Ethanesulfonic Acid

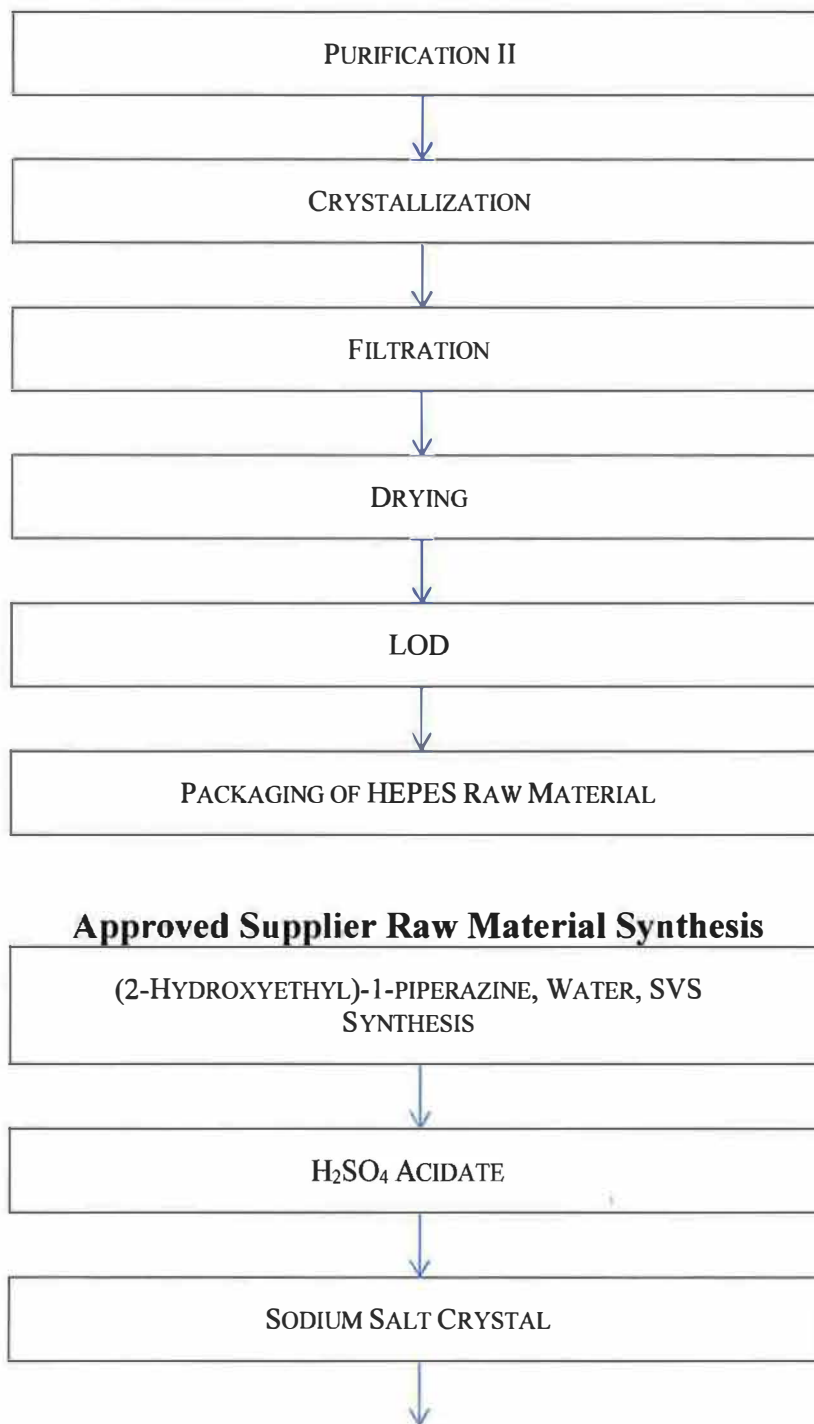
1.3.4. Morphological Form:

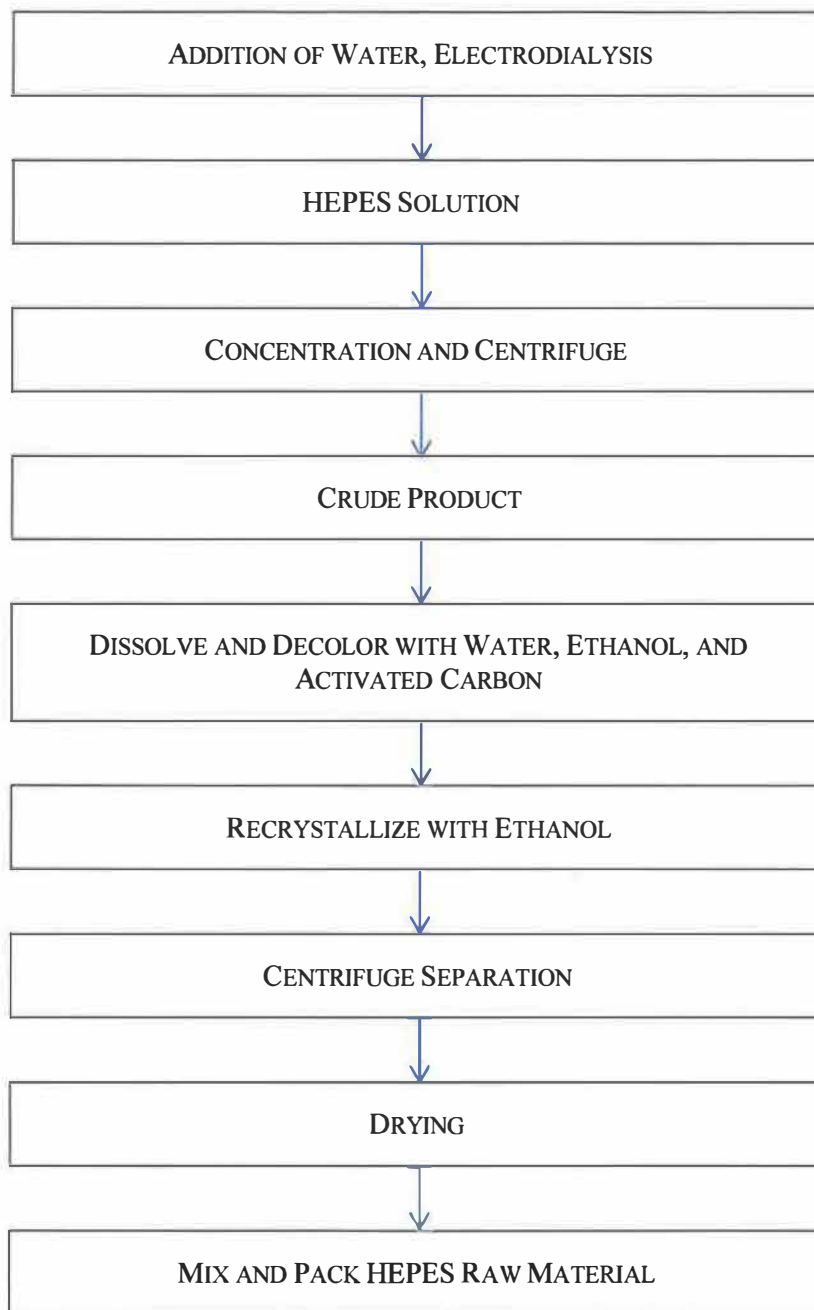
1.3.4.1. White / Crystals

1.3.5. Manufacturing Process:

1.3.5.1. The manufacturing process for HEPES is performed by the following:

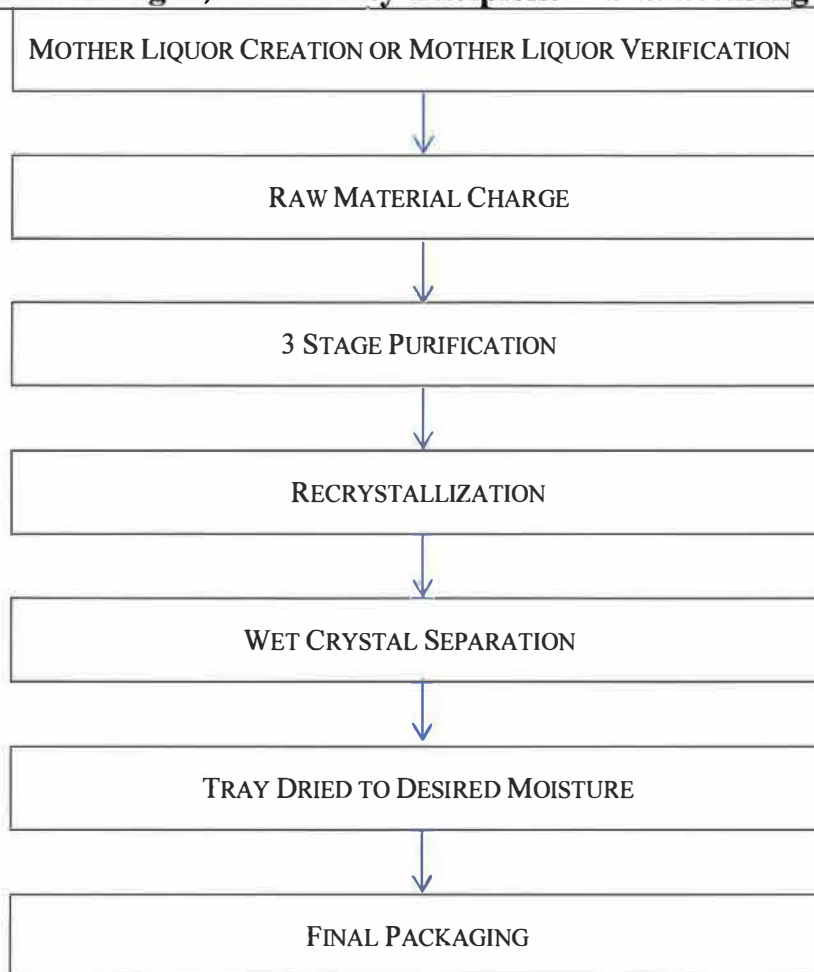




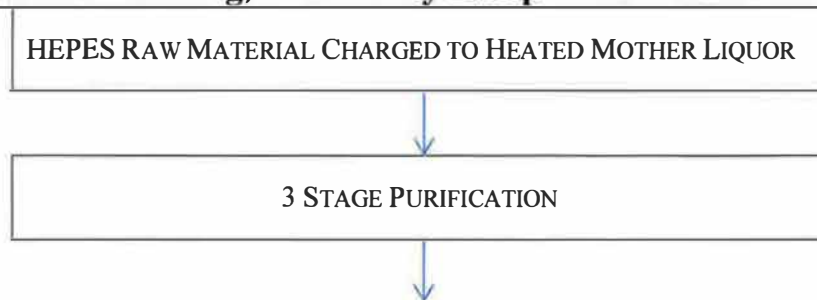


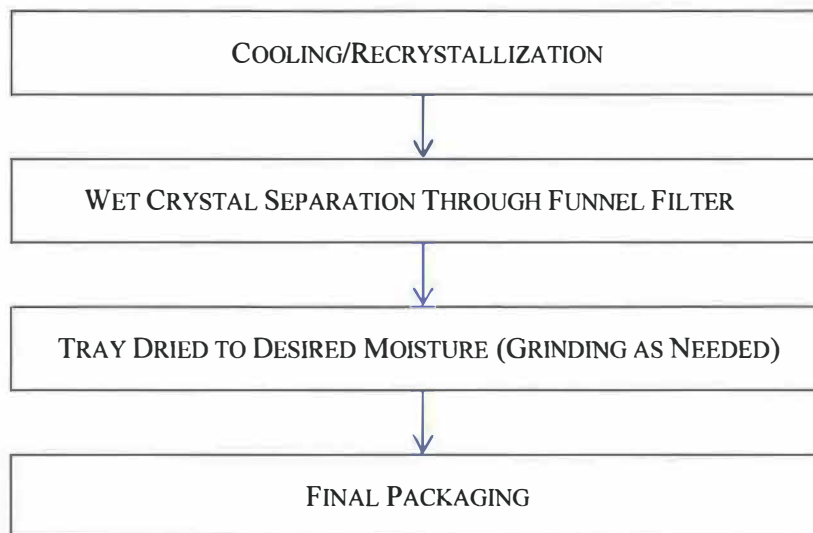


BioSpectra Bangor, PA Facility Excipient Manufacturing Process



BioSpectra Stroudsburg, PA Facility Excipient Manufacturing Process





1.3.6. Specifications:

1.3.6.1. Available upon request.

1.4. Regulatory Information:

1.4.1. Compendial Compliance:

1.4.1.1. Not Applicable

1.4.2. Master File:

1.4.2.1. Drug Master File (DMF) is currently not available for this product.

1.4.2.2. EDQM Certificate of Suitability is currently not available for this product.

1.4.3. REACH:

1.4.3.1. Refer to the HEPES Safety Data Sheet for the REACH Number or contact your Commercial Team Representative for further information.

1.4.4. BSE/TSE Statement:

1.4.4.1. HEPES, Bio Excipient Grade is a synthetic chemical and has been evaluated for the source of the raw materials used in its production through the Supplier Qualification Program. BioSpectra can state that BSE/TSE is not a concern based on this evaluation.

1.4.5. Allergens Statement:

1.4.5.1. HEPES, Bio Excipient Grade manufactured at BioSpectra and its raw materials are not manufactured with or using any of the following substances: Cereals containing gluten (i.e., wheat, rye, barley, oats, spelt, kamut or their hybridized strains) and products thereof, Crustaceans and products thereof, Eggs and products thereof, Fish and products thereof, Peanuts and products thereof, Soybeans and products thereof, Milk and products thereof (including lactose), Celery and products thereof, Mustard and products thereof, Sesame seeds and products thereof, Lupin and products thereof, Molluscs and products thereof, Sulphur dioxide and sulfites at >10 mg/kg as SO₂, Nuts, i.e., Almonds (*Amygdalus communis* L.), Hazelnuts (*Corylus avellana*), Walnuts (*Juglans regia*), Cashews (*Anacardium occidentale*), Pecan nuts (*Carya illinoensis* (Wangenh.) K. Koch), Brazil nuts (*Bertholletia excelsa*), Pistachio nuts (*Pistacia vera*), Macadamia or Queensland nuts (*Macadamia ternifolia*) and products thereof, Beef, Chicken, Pork, Azo Dyes, Benzoic Acid, Tartrazine, Vanillin, Cocoa, Cinnamon, Coriander, Yeast, Glutamate, Legumes, and Corn. BioSpectra has evaluated the raw material supply through the Supplier Qualification Program.

1.4.6. Genetically Modified Organisms (GMO) Statement:

1.4.6.1. HEPES, Bio Excipient Grade is a synthetic chemical and has been evaluated for the source of the raw materials used in its production through the Supplier Qualification Program. BioSpectra can state that genetic modification is not a concern based on this evaluation.

1.4.7. Residual Solvents Statement:

1.4.7.1. BioSpectra can state based on the manufacturing process and the controlled handling, storage, and analysis of this product, that the HEPES manufactured at BioSpectra complies with the requirements and specifications listed in the current USP method <467> Tables 1, 2, 3, or 4. BioSpectra does not intentionally add or use any solvents in the manufacturing process of HEPES, Bio Excipient Grade. BioSpectra has evaluated the raw material supply through the Supplier Qualification Program and can state that the Class 2 solvent Methanol, and the Class 3 solvent Ethanol are used in the manufacture of the HEPES raw material supplied to BioSpectra. BioSpectra's approved Raw Material Suppliers have stated that the HEPES raw material complies with the allowed limits of 3000ppm Methanol, or 5000ppm Ethanol. BioSpectra analyzed HEPES finished good for residual solvents during process validation, and has confirmed that the product complies with the limits of 3000ppm max Methanol, and 5000ppm max Ethanol.

1.4.8. Metal Catalyst and Metal Reagent Residues Statement:

1.4.8.1. HEPES, Bio Excipient Grade manufactured by BioSpectra is manufactured without the use of metal catalysts and metal reagents. BioSpectra has evaluated the raw material supply through the Supplier Qualification Program.

1.4.9. Pallet Statement:

1.4.9.1. BioSpectra can state that all wooden pallets used in the packaging and shipping of HEPES manufactured at BioSpectra are ISPM 15 compliant.



1.4.10. Elemental Impurities Statement:

1.4.10.1. BioSpectra's HEPES, Bio Excipient Grade material has been profiled for elemental impurities via ICP utilizing USP <232> and <233> in accordance with ICH Q3D. The results are reported in the associated Elemental Impurity Profile and are available upon request.

1.4.11. Melamine Statement:

1.4.11.1. BioSpectra does not intentionally add or use melamine in the BioSpectra manufacturing process of HEPES, Bio Excipient Grade. BioSpectra has evaluated the raw material supply through the Supplier Qualification Program and can state that the raw materials are not expected to contain melamine based on this evaluation. BioSpectra analyzes HEPES annually for Melamine, with a specification of 2.5mg/kg max.

1.5. Miscellaneous Product Information:

1.5.1. Description of Batch:

1.5.1.1. The HEPES process is a batch process where expected batch yields are established during validation in accordance with the Manufacturing Process Validation Master Plan. Individual batch yield is additionally determined for each manufactured batch and documented in the respective batch record.

1.5.2. Lot/batch numbering system:

1.5.2.1. The lot numbering system at BioSpectra employs the following format: 4 alphanumeric digits followed by a hyphen, 4 numerical digits followed by a hyphen, and finally 5 numerical digits. A sample lot number would appear as: HEPE-0123-00001, or HEPE-0223-00001.

1.5.2.1.1. The first four digits are alpha digits which indicate the material manufactured, where HEPE represents HEPES. The fifth and sixth digits are numeric digits which indicate the site of final packaging, where 01 represents the Bangor, PA facility, and 02 represents the Stroudsburg, PA facility. The seventh and eighth digits are numeric digits which indicate the year the batch record was issued, where 23 represents 2023. The final five digits are numeric digits which indicate the sequential batch number, where 00001 represents the first HEPES batch of 2023 that is automatically generated by the ERP system. The sequential batch number automatically resets on the first of the new calendar year.

1.5.3. Expiration date and/or recommended re-evaluation interval:

1.5.3.1. The current recommended Retest or Expiration Date for HEPES, Bio Excipient Grade is available in the BioSpectra Product Retest and Expiration Date List, DCN: BSI-LST-0239, and is based on current available stability data in accordance with BioSpectra's Stability Testing Program. Additionally, the recommended Retest or Expiration Date will be available on the Product Specific Certificate of Analysis, as applicable.

1.5.4. Storage and shipping conditions:

1.5.4.1. Keep container tightly closed in a dry and well-ventilated place.



1.5.5. Packaging:

1.5.5.1. Packaging information is available through the following:
<https://Biospectra.us/packaging>

1.6. Contact Information:

1.6.1. <https://www.biospectra.us/about-us/commercial-marketing-team>