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BIOSPECTRA'S TRIS RAW MATERIAL NITROSAMINE COMPLIANCE STATEMENT

INTRODUCTION: The following serves as a statement of compliance for the control of nitrosamine impurities in BioSpectra's Tris Raw Material utilized in the Tromethamine API manufacturing process.

SCOPE: A risk assessment for Nitrosamine, in accordance with European Medicines Agency (EMA) expectations, has been conducted by BioSpectra's Approved Raw Material Supplier of Tris Raw Material used in the manufacture of Tromethamine API.

RESULTS: BioSpectra's Approved Supplier has identified five organic impurities expected to be present in the Tris Raw Material. These components and their expected percent weight are detailed in Table 1 below.

Table 1. Tris Raw Material Expected Organic Impurities

Component	Wt. %
2-amino-1,3-propanediol (APD)	<0.020
2-amino-2-methyl-1,3-propanediol (AMPD)	<0.0014
2-(N-methylamino)-1,3-propanediol (MMAPD)	<0.030
2-(N-methylamino)-2-hydroxymethyl-1,3-propanediol (MMTA)	<0.030
2-(N,N-dimethylamino)-2-hydroxymethyl-1,3-propanediol (DMTA)	<0.0021

Nitric Acid, Nitrous Acid, Nitric Oxide, and Organic Nitrites are substances that can be used in the Tris Raw Material manufacturing process, which are identified by the EMA as potential sources of nitrosamine impurities. These substances may be present during the same, preceding, or subsequent processing steps as amines or amides. The potential risk of nitrosamines in the Tris Raw Material manufacturing process or Tris Raw Material is mitigated through in-process controls over the manufacture, purity, or impurity profile of intermediates during the manufacturing process.

Tris Raw Material has been analyzed by BioSpectra's Supplier, with analytical data confirming the lack of nitrosamines found in any quantifiable level in the finished product, with a 20ppb limit of detection. The supplier confirms to have analytical data which shows that the Tris Raw Material does not contain the nitrosamines principally attributed to the presence of the specific nitrosating species indicated.

CONCLUSION: Nitrosamines are not anticipated to be present in Tris Raw Material, as indicated in the 2020 letter response to the request to evaluate the risk of the presence of nitrosamine impurities in the Tris Raw Material products supplied by the Approved Supplier to BioSpectra.

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