Quality & Regulatory Affairs
ashland.com

NUMBER EI-20161024-001-DSD-V02

Elemental Impurities Statement

Natrosol™ hydroxyethylcellulose

Ashland's Commitment to a Risk-Based Approach

Elemental impurities in drug products may arise from several sources; they may be residual catalysts that were added intentionally in synthesis or may be present as impurities (e.g., through interactions with processing equipment or container/closure systems or by being present in components of the drug product). Because elemental impurities do not provide any therapeutic benefit to the patient, their levels in the drug product should be controlled within acceptable limits as defined by the International Council for Harmonization's (ICH) Q3D Guideline for Elemental Impurities (16 December 2014).

ICH Q3D recommends final drug manufacturers conduct a product risk assessment by first identifying known and potential sources of elemental impurities. Manufacturers should consider all potential sources of elemental impurities, such as elements intentionally added, elements potentially present in the materials used to prepare the drug product, and elements potentially introduced from manufacturing equipment or container closure systems. Manufacturers should then evaluate each elemental impurity likely to be present in the drug product by determining the observed or predicted level of the impurity and comparing it with the established permitted daily exposure (PDE).

The US Food & Drug Administration (FDA) has also issued guidance for industry on Elemental Impurities in Drug Products (June 2016) to provide recommendations to implement both the ICH Q3D guidelines as well as comply with new general chapters introduced by the U.S. Pharmacopeial Convention (USP). The USP introduced new limits and analytical procedures for elemental impurities in General Chapters <232> Elemental Impurities—Limits and <233> Elemental Impurities—Procedures. Their primary goals are to (1) set limits for acceptable levels of elemental impurities in finished drug products, and (2) update the methodology used to test for elemental impurities in drug products to include modern analytical procedures.

Ashland is committed to assisting our partners gain sufficient knowledge of Ashland's products' contribution to elemental impurities in applying a risk-based approach to assessing the final drug product's compliance with PDE limits. The following information is provided based on our knowledge of raw materials, manufacturing process and, as needed, to a limited extent, testing of our products for elemental impurities. Please note, testing for elemental impurities is not required under the ICH Q3D guidelines as they recommend a risk-assessment approach. USP worked closely with ICH to align its new General Chapters with ICH Q3D and General Chapter <232> endorses a risk-based approach to the control of elemental impurities such as described in ICH Q3D. Ashland will follow the harmonized approach and rely on risk-assessment as opposed to testing for elemental impurities.

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Effective Date

03-MAR-2017

Supplier and Manufacturer Information

Supplier Identity	Ashland Industries Netherlands BV	**Manufacturer Identify**	Ashland Industries Netherlands BV
Supplier Address	Noordweg 9, 3336 LH, Zwijndrecht, Netherlands	**Manufacturer Address**	Noordweg 9, 3336 LH, Zwijndrecht, Netherlands

Material Information

Material Name Natrosol™ hydroxyethylcellulose

Source/Type of Excipient ☐ Mineral ☐ Mineral derived ☐ Plant ☒ Plant derived ☐ Synthetic ☐ Fermentation derived

Other (explain)

Elemental Impurities

Elemental Impurity		Class	Likely to be Present			Intentionally Added as catalysts/ reagents/processing aids		If Known, Please Identify the Expected Concentration /Units (or Range)	Analytical Method Used (and Limit of Detection if Available)	Comments regarding source of information (i.e.; frequency of testing, process understanding, etc.)
Arsenic (inorganic)	As	1	Yes ☒	No ☐	Unknown ☐	Yes ☐	No ☒	<0.4 ppm	LOD 0.1	Random samples tested over 20 years by various analytical techniques.
Cadmium	Cd	1	Yes ☐	No ☒	Unknown ☐	Yes ☐	No ☒			

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Mercury (inorganic)	Hg	1	Yes ☒	No ☐	Unknown ☐	Yes ☐	No ☒	<0.5 ppm	LOD 0.3	Random samples tested over 20 years by various analytical techniques.
Lead	Pb	1	Yes ☒	No ☐	Unknown ☐	Yes ☐	No ☒	<0.5 ppm	LOD 0.2	Random samples tested over 20 years by various analytical techniques.
Cobalt	Co	2A	Yes ☐	No ☒	Unknown ☐	Yes ☐	No ☒			
Nickel	Ni	2A	Yes ☐	No ☒	Unknown ☐	Yes ☐	No ☒			
Vanadium	V	2A	Yes ☐	No ☒	Unknown ☐	Yes ☐	No ☒			
Silver	Ag	2B	Yes ☐	No ☒	Unknown ☐	Yes ☐	No ☒			
Gold	Au	2B	Yes ☐	No ☒	Unknown ☐	Yes ☐	No ☒			
Iridium	Ir	2B	Yes ☐	No ☒	Unknown ☐	Yes ☐	No ☒			
Osmium	Os	2B	Yes ☐	No ☒	Unknown ☐	Yes ☐	No ☒			
Palladium	Pd	2B	Yes ☐	No ☒	Unknown ☐	Yes ☐	No ☒			
Platinum	Pt	2B	Yes ☐	No ☒	Unknown ☐	Yes ☐	No ☒			
Rhodium	Rh	2B	Yes ☐	No ☒	Unknown ☐	Yes ☐	No ☒			
Ruthenium	Ru	2B	Yes ☐	No ☒	Unknown ☐	Yes ☐	No ☒			
Selenium	Se	2B	Yes ☐	No ☒	Unknown ☐	Yes ☐	No ☒			
Thallium	Tl	2B	Yes ☐	No ☒	Unknown ☐	Yes ☐	No ☒			

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Barium	Ba	3	Yes ☐	No ☒	Unknown ☐	Yes ☐	No ☒			
Chromium	Cr	3	Yes ☐	No ☒	Unknown ☐	Yes ☐	No ☒			
Copper	Cu	3	Yes ☒	No ☐	Unknown ☐	Yes ☐	No ☒	<0.6 ppm	LOD 0.4	Random samples tested over 20 years by various analytical techniques.
Lithium	Li	3	Yes ☐	No ☒	Unknown ☐	Yes ☐	No ☒			
Molybdenum	Mo	3	Yes ☐	No ☒	Unknown ☐	Yes ☐	No ☒			
Antimony	Sb	3	Yes ☐	No ☒	Unknown ☐	Yes ☐	No ☒			
Tin	Sn	3	Yes ☐	No ☒	Unknown ☐	Yes ☐	No ☒			

For Additional Support

For additional information, please contact your Ashland account representative.

Reference Standards and Guidances

International Council for Harmonization's (ICH) Q3D Guideline for Elemental Impurities (16 December 2014)
U.S. Pharmacopeial Convention (USP) General Chapters <232> Elemental Impurities—Limits and <233> Elemental Impurities—Procedures (May 2015)

Document Control

Effective Date of Change	Description of Change	Change Reviewed and Approved by
April 6, 2015	Created	P. Zawislak
October 24, 2016	Updated Ashland logo. Removed expected concentration and analytical method as elements are not expected to be present based on raw material, manufacturing process and limited test data.	L. Galati

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March 3, 2017	Added data for elemental impurities expected to be present in product.	D. Dennis