BIOTECH

Statement of Compliance

USTR 3822

Material Safety Statement for Pall Allegro™ Single-Use Systems

Version Number: 1.0
Date: January 30, 2023
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Disclaimer: This document was released having been reviewed and approved through Pall's Quality and Regulatory Approval process. The principal author of this document is responsible for collating, from subject matter experts, the technical data and information presented. All information is brought together to be accurate to the best of our knowledge at the time of approval.

Biocompatibility

All fluid path contact materials comply with United States Pharmacopoeia (USP) <88> Biological Reactivity Test, *in vivo*, Class VI or the equivalent International Organization for Standardization (ISO) tests (ISO 10993-6 *Biological evaluation of medical devices Part 6: Tests for local effects after implantation*, ISO 10993-10 *Biological evaluation of medical devices Part 10: Tests for irritation and skin sensitization* and ISO 10993-11 *Biological evaluation of medical devices Part 11: Tests for systemic toxicity*).

Compliance with these requirements is based on tests performed by Pall or based on information provided by our suppliers.

E962 Pall Global Disallowed and Controlled Substances

Pall controls or limits the use of various substances in the materials used to manufacture our products, based on international regulatory and legislative guidance as well as specific customer concerns. Pall maintains a global purchasing specification 'Supplier Guidance on Disallowed and Controlled Substances (E962)' with our material suppliers whereby, suppliers are required to notify us if any identified substances are present in the items they supply.

Compliance to EU Regulation (EC) No. 1907/2006 [Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)]

Pall Allegro single-use systems are considered 'complex objects' comprised of 'component articles' under the REACH regulations. These products do not contain authorized substances found in Annex XIV ('List of substances subject to authorisation') nor any substances subject to Annex XVII restrictions ('Restrictions'). With respect to the REACH candidate list of 'Substances of Very High Concern' (SVHC), with the exception of the below, component articles do not contain SVHCs at a concentration of greater than 0.1% by weight.

Substances of Very High Concern

Some Allegro single-use systems may include one or more silicone components which contain the following candidate listed SVHCs above 0.1% by weight:

Compound Name	CAS* Number
Octamethylcyclotetrasiloxane (D4)	556-67-2
Decamethylcyclopentasiloxane (D5)	541-02-6
Dodecamethylcyclohexasiloxane (D6)	540-97-6

**CAS: Chemical Abstracts Service*

These cyclosiloxane compounds are commonly used in the production of silicone-based materials throughout the industry. Please note that the REACH regulations do not place restrictions or conditions of use on silicone polymers containing D4, D5, or D6 siloxanes above 0.1% by weight. In line with the requirements of Waste Framework Directive 2008/98/EC Article 9(1)(i) as amended by 2018/851/EU, the component articles and the complex objects using these components are listed in the ECHA database for 'Substances of Concern in Products' (SCIP).

Compliance to European Directives on Restriction of Hazardous Substances (RoHS)

European Directive: 'RoHS2' (2011/65/EU) and 'ROHS3' amendment 2015/863, plus UK implementation statues, restrict the use of the ten hazardous substances below in various types of electronic and electrical equipment placed on the market in the European Union and UK. Although single-use systems are neither electrical nor electronic devices, Pall provides information on these substances to assist users employing our products in the manufacture of electrical or electronic equipment:

- Lead
- Cadmium
- Mercury
- Hexavalent chromium
- Polybrominated biphenyl (PBB)
- Polybrominated diphenyl ether (PBDE)
- Bis(2-ethylhexyl) phthalate (DEHP)
- Benzyl butyl phthalate (BBP)
- Dibutyl phthalate (DBP)
- Diisobutyl phthalate (DIBP)

Minimization of Transmissible Spongiform Encephalopathy (TSE) and Transmission of Bovine Spongiform Encephalopathy (BSE)

Materials of direct animal origin i.e., animal parts, tissues, or body fluids, are not knowingly employed.

Single-use systems are assembled from components using polymeric resin materials that may contain trace ingredients that are derived from materials of animal origin. These materials do not present a risk of TSE/BSE based on their source (sourcing considers animal species, tissue, and country of origin) and/or exposure to processing conditions known to inactivate infectious agents associated with TSE/BSE diseases.

Tallow-Derivatives

Some polymeric resin manufacturers employ trace levels of additives in the resin formulation. These additives may be manufactured using animal tallow as a starting substance ('tallow-derivatives'). The tallow may have been sourced from bovine species or, less commonly, from non-TSE relevant species. Please be advised that bovine tallow derivatives are considered low risk material for TSE/BSE according to the current revision of the U.S. Code of Federal Regulations, Title 21 Part 189.5 Substances Prohibited from use in Human food; Sub part B: Prohibited cattle material: paragraph a7. Furthermore, the European Medicines Agency's (EMEA) Committee for Medicinal Products for Human Use (CHMP) 'Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products' (EMEA 410/01 Rev 3, 2011), and other international guidelines, gives specific consideration to tallow derivatives and states that they are unlikely to be infectious if rigorously processed during their manufacture (for example, hydrolysis or transesterification, at no less than 200 °C under pressure for no less than 20 minutes). Our suppliers have stated that their raw materials have been processed under conditions at least as rigorous as these.

Pall Corporation continuously works to assure the safety of our products with respect to potential BSE/TSE transmission by working through our supply chain to obtain information regarding the possible use of animal-based material.

Product Substances / Compounds

Please be advised that Pall does not intentionally use or specify the use of the following substances/compounds and unless specifically stated, does not routinely analyze our products for their presence.

Allergenic Substances

These products are not packaged food items or foodstuffs and therefore are not in scope of the U.S. Food and Drug Administration's Food Allergen Labeling and Consumer Protection Act of 2004 or the European Directive 2003/89/EC, which deals with labeling for the presence of common allergenic ingredients. However, we can state that the following substances as defined in the regulations are not direct materials of construction or knowingly utilized by Pall in their manufacture:

- Celery (root, leaves, stalk, not seeds)
- Cereals containing gluten (i.e., wheat, rye, barley, oats, spelt, kamut or their hybridized strains)
- Crustaceans
- Eggs or egg products (whites, yolks, meringue, mayonnaise, etc.)
- Fish (cod, flounder, salmon, trout, tuna, etc.)
- Lupin
- Milk and milk (dairy) derivatives
- Mollusks
- Mustard
- Peanuts or peanut products (butter, oil, flour)
- Sesame seeds
- Soy bean or soy products (soy derived vegetable protein, tofu, etc.)
- Tree nuts (including almond, brazil, cashew, chestnut, filbert or hazelnut, hickory, macadamia, pecan, pine, pistachio, queensland or walnut)
- Sulfur dioxide and sulfites, at concentrations greater than 10 mg/kg or 10 mg/L expressed as SO_2

Please be advised that the raw materials we purchase are not certified as 'allergen free'. Therefore, we cannot exclude the possibility that an allergenic substance may be present in trace quantities deriving from a raw material manufacturing process.

Bisphenol A (BPA)

Single-use systems may incorporate various components utilizing materials including polycarbonate and polysulfone in which BPA is used as a primary building block in the polymer synthesis. Unreacted monomer or BPA from polymer degradation may be present in the polymer matrix of these materials at trace levels.

Elemental Impurities

The United States Pharmacopeia (USP <232> Elemental Impurities – Limits) and Food and Drug Administration (FDA) / International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q3D(R1) Elemental Impurities: Guidance for Industry (Mar 2019) specify limits for elemental impurities in final drug products. Elemental impurities may arise from residual catalysts intentionally added during polymer synthesis or be present as impurities related to process equipment. Twenty-four (24) elements are defined, that if known to be present, intentionally added, or have the potential to be introduced, must be below concentration limits or Permitted Daily Exposures (PDE) in the final drug product. These elements are assigned into three classes based on their toxicity profile and the likelihood of them persisting into a drug product, with Class 1 being the most toxic.
While the concentration limits or PDE expressed in the above referenced documents do not apply directly to process equipment or single-use system components, Pall is pleased to provide you with the following information to assist in your risk assessment and control strategies.

All Q3D Class 1 elements, and some Class 2 and Class 3 elements, are not expected to be present in Pall product materials of construction.

Phthalates

Pall final products meet current requirements under the REACH and RoHS regulations for phthalates (i.e., no phthalate plasticizers are known to be present at a concentration of greater than 0.1% (w/w) in these products, individually or as a combination, for the restricted phthalates).

Residual Solvents Risks

Class 1 solvents as defined in ICH Q3C(R8) are not used during the manufacture of single-use systems. Therefore, we do not expect Class 1 residual solvents to be present in our products.

Pall manufacturing processes may involve the use of isopropanol and ethanol (Class 2 or Class 3) solvents, with subsequent processing steps greatly reducing any residual levels.

Natural Latex

Natural rubber latex is not knowingly used in single-use systems.

Melamine

Melamine or any of the ‘at-risk’ components for melamine contamination identified in FDA’s Guidance for Industry – Pharmaceutical Components at Risk for Melamine Contamination (August 2009), are not utilized in the manufacturing processes of single-use systems.

Genetically Modified Organisms (GMOs)

The fluid contact components of single-use systems are constructed from primary materials which are polymeric in nature. However, since the raw materials we purchase are not certified as ‘non-GMO’, we cannot exclude the possibility that genetically modified material may be present in a trace quantity as an incidental additive deriving from the raw material manufacturing process.

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Pall Corporation has offices and plants throughout the world. To locate the Pall office or distributor nearest you, visit www.pall.com/contact.

The information provided in this literature was reviewed for accuracy at the time of publication. Product data may be subject to change without notice. For current information consult your local Pall distributor or contact Pall directly.

USTR 3822 Version 1.0
January 2023