Biological Evaluation of:

Knitted Socks

Contents

Biocompatibility evaluation carried out by (*names, job titles and qualifications*):
- Mattia Rampazzo, EU Product manager and EU Regulatory assistant. Over 10 years experience as product manager; experience in preparation of 4 technical files compliant to the MDR2017/745, including 2 Clinical Evaluations.

1. General information

Device:	Knitted Socks
Ref. nr:	CB 1 ply, CB 3 ply, CB 5 ply, CB 6 ply, KC 1 ply, KC 1 ply hole, KC 3 ply, KC 3 ply hole, KC 5 ply, KC 5 ply hole
Intended use:	The prosthetic sock helps to maintain appropriate position of the residual limb inside the prosthesis. In addition, the prosthetic sock protects and cushions the skin, absorbs perspiration, and helps in reducing friction between the prosthesis and the residual limb.
Lifetime claimed:	None
Storage conditions:	Not relevant

2. Categorization according ISO 10993-1:2009, chapter 5

Nature of body contact	**Duration of contact** (A) < 24h	(B) 24h - 30d	(C) > 30d
Does not contact body directly of indirectly	Primary application: socks is worn outside a prosthetic liner		
Surface-contacting devices:			
a) Skin: *e.g. electrodes, external prostheses, fixation tapes, compression bandages, etc.*	May occur		
b) Mucosal membranes: *e.g. contact lenses, urinary catheters, intravaginal devices, endotracheal tubes, etc.*	Does not apply		
c) Breached or compromised surfaces: *e.g. dressings, healing devices and occlusive patches for ulcers, burns, etc.*	Does not apply		
External communicating devices:			
a) Blood path, indirect: *e.g. solution administration-, extension-, transfer sets and blood administration sets*	Does not apply		
b) Tissue/bone/dentin: *e.g. laparoscopes, arthroscopes, draining systems, dental cements, etc.*	Does not apply		
c) Circulating blood: *e.g. intravascular catheters, temporary pacemaker electrodes, oxygenators, dialysers*	Does not apply		
Implant devices:			
a) Tissue/bone: *e.g. orthopaedic pins, plates, drug supply devices, neuromuscular sensors*	Does not apply		
b) Blood: *pacemaker electrodes, artificial arteriovenous fistulae, heart valves, vascular grafts*	Does not apply		

3. Test selection

Following selection applies: (Highlight)

Body contact		Contact Duration **A** = Limited **B** = Prolonged **C** = Permanent	Cytotoxicity	Sensitization	Irritation or intra-cutaneous reactivity	Systemic toxicity (acute)	subchronic toxicity (Subacute toxicity)	Genotoxicity	Implantation	Haemo-compatibility	USP Classification[1]
Surface Devices	Skin	A	X	X	X						I
		B	X	X	X						I
		C	X	X	X						I
	Mucosal membrane	A	X	X	X						I
		B	X	X	X						III
		C	X	X	X		X	X			V
	Breached or compromised surfaces	A	X	X	X						III
		B	X	X	X						V
		C	X	X	X		X	X			VI
Externally Communicating Devices	Blood Path, indirect	A	X	X	X	X				X	IV
		B	X	X	X	X				X	V
		C	X	X		X	X	X		X	VI
	Tissue / Bone / Dentin	A	X	X	X						IV
		B	X	X	X	X	X	X	X		VI
		C	X	X	X	X	X	X	X		VI
	Circulating Blood	A	X	X	X	X				X	IV
		B	X	X	X	X	X	X	X	X	VI
		C	X	X	X	X	X	X	X	X	VI
Implant Devices	Tissue / bone	A	X	X	X						VI
		B	X	X	X	X	X	X	X		VI
		C	X	X	X	X	X	X	X		VI
	Blood	A	X	X	X	X	X		X	X	VI
		B	X	X	X	X	X	X	X	X	VI
		C	X	X	X	X	X	X	X	X	VI

Source ISO 10993:-1:2009, Annex A, Table A.1

No test is deemed to be necessary
Rationale:

- Knitted socks are primarily used outside a prosthetic liner, not in direct contact with the skin. Contact with intact skin may occur if the patient will use the sock during rest time, while not wearing the prosthetic leg.
- Market experience. The device has been on the market for more than 12 years, with an approx. turnover of 500,000 units/year. No serious incident and no field safety corrective action has been reported on the subject device or on similar devices. See 820263 (A) - C8.2-8_v0.1 PMS - PSUR Report (MDR) and Knitted Socks_820284 (A) - STED118a Clinical Evaluation Report v0.1.
- No complaint on skin irritation has been reported to the manufacturer. See 820263 (A) - C8.2-8_v0.1 PMS - PSUR Report (MDR) and Knitted Socks_820284 (A) - STED118a Clinical Evaluation Report v0.1.
- Literature search has been performed and has identified no biocompatibility hazards and no undesirable side-effects. See Knitted Socks_820284 (A) - STED118a Clinical Evaluation Report v0.1.
- The overall risk of the device is low- 2 residual risks resulting from Risk Management, both accepted because of low risk and low frequency have been identified 820281 (A) - STED103 v0.1 Risk Management Report - Knitted Socks
- Risk/benefit profile is acceptable.

[1] United States Pharmacopoeia classification

4. Available standards[2]

ISO 10993 consists of the following parts, under the general title Biological evaluation of medical devices:

- Part 1: Evaluation and testing within a risk management process
- Part 2: Animal welfare requirements
- Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity
- Part 4: Selection of tests for interactions with blood
- Part 5: Tests for in vitro cytotoxicity
- Part 6: Tests for local effects after implantation
- Part 7: Ethylene oxide sterilization residuals
- Part 9: Framework for identification and quantification of potential degradation products
- Part 10: Tests for irritation and skin sensitization
- Part 11: Tests for systemic toxicity
- Part 12: Sample preparation and reference materials
- Part 13: Identification and quantification of degradation products from polymeric medical devices
- Part 14: Identification and quantification of degradation products from ceramics
- Part 15: Identification and quantification of degradation products from metals and alloys
- Part 16: Toxicokinetic study design for degradation products and leachables
- Part 17: Establishment of allowable limits for leachable substances
- Part 18: Chemical characterization of materials
- Part 19: Physico-chemical, morphological and topographical characterization of materials (Technical Specification)
- Part 20: Principles and methods for immunotoxicology testing of medical devices (Technical Specification)

Biological Risks	Acceptable EN-ISO Standard	Acceptable ISO Standard
Cytotoxicity	EN ISO 10993-5:2009	idem
Sensitization	EN ISO 10993-10:2013	ISO 10993-10:2010
Irritation	EN ISO 10993-10:2013	ISO 10993-10:2010
Acute Systemic Toxicity	EN ISO 10993-11:2009	ISO 10993-11:2006
Subchronic Toxicity	EN ISO 10993-11:2009	ISO 10993-11:2006
Genotoxicity	EN ISO 10993-3:2014	idem
Implantation	EN ISO 10993-6:2009	ISO 10993-6:2007
Haemocompatibility	EN ISO 10993-4:2009	ISO 10993-4:2002, incl. Amd 1:2006
Chronic Toxicity	EN ISO 10993-11:2009	ISO 10993-11:2006
Carcinogenicity	EN ISO 10993-3:2014	idem
Reproductive	EN ISO 10993-3:2014	idem
Biodegradation	EN ISO 10993-9:2009	ISO 10993-9:2009
Other:		
Ethylene oxide sterilization residuals	EN ISO 10993-7:2008/AC:2009	idem
Sample preparation	EN ISO 10993-12:2012	idem
Degradation Polymeric	EN ISO 10993-13:2010	idem
Degradation Ceramics	EN ISO 10993-14:2009	ISO 10993-14:2001
Degradation Metals	EN ISO 10993-15:2009	ISO 10993-15:2000
Toxicokinetic study	EN ISO 10993-16:2010	Idem
Limits for leachable substances	EN ISO 10993-17:2009	ISO 10993-17:2002
Chemical characterization	EN ISO 10993-18:2009	ISO 10993-18:2005

[2] Source: http://ec.europa.eu/growth/single-market/european-standards/harmonised-standards/medical-devices/index_en.htm

5. Physical effects

Physical effects of the device are considered (if they impact the biocompatibility) according to ISO 10993-19.

	Information:
Porosity	
Classical	Does not apply -No impact on biocompatibility
Connectivity	Does not apply -No impact on biocompatibility
Scaffolds	Does not apply -No impact on biocompatibility
Morphology	
Crystallinity	Does not apply -No impact on biocompatibility
Amorphous	Does not apply -No impact on biocompatibility
Multiple phases	Does not apply -No impact on biocompatibility
Hard/soft surfaces	Does not apply -No impact on biocompatibility
Surface energy/charge	
Hydrophobic	Does not apply -No impact on biocompatibility
Hydrophylic	Does not apply -No impact on biocompatibility
Protein adsorption	Does not apply -No impact on biocompatibility
Protein repulsion	Does not apply -No impact on biocompatibility
Abrasion resistance	
Stability of treated surface	Does not apply -No impact on biocompatibility
Surface friction	Does not apply -No impact on biocompatibility
Topography	
Surface chemical mapping	Does not apply -No impact on biocompatibility
Roughness (smooth, pitted, grooved, irregular terrain, textured)	Does not apply -No impact on biocompatibility Does not apply -No impact on biocompatibility
Particles	
Size	Does not apply -No impact on biocompatibility
Size distribution	Does not apply -No impact on biocompatibility
3D shape	Does not apply -No impact on biocompatibility
Shape and Form	
Shape and Form	Does not apply -No impact on biocompatibility
Swelling	
Water absorption	Does not apply -No impact on biocompatibility
Solvent absorption	Does not apply -No impact on biocompatibility
Shape change	Does not apply -No impact on biocompatibility
Surface crazing	Does not apply -No impact on biocompatibility
Weight gain	Does not apply -No impact on biocompatibility

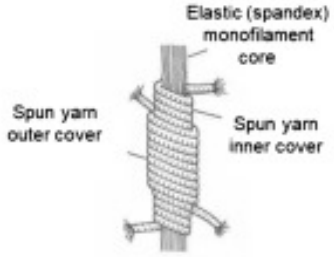
6. Manufacturing

List of manufacturing steps, see separate flowchart in STED.

Coolmax Yarns are knitted on a flatbed knitting machine to create a prosthetic sock
Prosthetic socks are then washed in pure water
Prosthetic socks are dried in a dryer and packed after final quality inspection

7. Material characterization

ALPS Knitted socks are entirely made of Coolmax. ALPS use a corespun coolmax yarn, composed of 98% Coolmax (Polyester) and 2% Lycra (elastic).
Structure of the Corespun yarn is shown below.



To assess the biocompatibility of the raw material used to manufacture the Knitted Socks, ALPS has:

- Selected only yarns OEKO-TEX100 Certified. Certificates for Elastane (Lycra) and Coolmax (Polyester) are saved in the supplier folder.
- Reviewed and analyzed the Safety Data Sheet of the materials, focusing on the exterior yarn (Polyester)

Finding from the analysis of the SDS are reported in the chart below and have been integrated into the product risk analysis.

SDS Section	Potential Hazard	Risk / Probability estimation
Hazards	Forming of combustible dust	Combustible dust not expected during normal or prolonged use
Composition	This fiber may have been produced with carbon black and/or titanium dioxide.	Carbon black and titanium dioxide are encapsulated into the polymer, not expected to be released during normal use
First Aid Measures	Skin: Fiber particles and dusts may be mechanically irritating to skin. While irritation is not expected under normal use, prolonged exposure and continuous rubbing of fiber particles on skin may produce skin irritation	Continuous dust-generating rubbing may occur in a very loose prosthetic socket (end user misuse). No evidence of such risk has emerged from the clinical evaluation or from the Post Market Surveillance
Handling / Toxicological information	When fiber products are cut, chopped, or manipulated in other similar handling methods, some dust may be produced. Do not breathe dust from this material	Product is not cut, chopped or manipulated during normal use
Regulatory information	Fire hazard	Not likely to happen under normal conditions of use

8. Risk Management

In a separate document (See: 820279 (B) - STED101 v0.1 Risk Management Procedure, according EN ISO 14971:2012), the manufacturer established, documents and maintains throughout the life-cycle an ongoing process for identifying hazards associated with a medical device, estimating and evaluating the associated risks, controlling these risks, and monitoring the effectiveness of the controls. This process includes the following elements:
– risk analysis;
– risk evaluation;
– risk control;
– production and post-production information.

Risk evaluation on materials

B.2.2.1a/b	**Intended use / device characteristics**
Material 01	**POLYESTER FIBER (Coolmax)**
Function in MD:	Fiber used to make the device (outer layer of the corespun yarn)
Weight percent:	98%
Foreseeable misuse:	Continuous dust-generating rubbing action due to the patient wearing a loose prosthetic socket for a prolonged period.
Physical characteristics:	Solid
Chemical characteristics:	**Chemical name** / **CAS number** / **%** POLYESTER FIBER / 25038-59-9 / 90-99% CARBON BLACK / 1333-86-4 / 0-5% TITANIUM DIOXIDE / 13463-67-7 / 0-5% FIBER LUBRICANT / / 0-2%
Material 02	SPANDEX / ELASTANE FIBER
Function in MD:	Fiber used to make the device (inner layer of the corespun yarn)
Weight percent:	2%
Foreseeable misuse:	None
Physical characteristics:	Solid
Chemical characteristics:	Spandex/Elastane: 100%

B.2.2.2a	**Biological hazard identification**
Hazards in: - materials	Carbon black and titanium dioxide are encapsulated into the polymer, not expected to be released during normal use
- additives	No additives from the manufacturing process. No additives from the materials SDS

- processing aids	None
- other potential leachables	None has been identified - Materials are OEKO-Tex Certified
- Impurities	None reported - Materials are OEKO-Tex Certified
B.2.2.2b	
Chemically-mediated hazards - toxicology data on component materials	When fiber products are cut, chopped, or manipulated in other similar handling methods, some dust may be produced.
- Dose-response relationship	Not available
- Nature of toxicity	Inhalation: Inhalation of dusts may cause irritation of the respiratory tract. Skin: Fiber particles and dusts may be mechanically irritating to skin. While irritation is not expected under normal use, prolonged exposure and continuous rubbing of fiber particles on skin may produce skin irritation. Eyes: Particles and dusts may be mechanically irritating when in contact with eyes. Symptoms include itching, burning, redness and tearing. Ingestion: Ingestion of this product may cause nausea, vomiting and diarrhea. Ingestion of large amounts of fibers may cause gastrointestinal blockage which can cause stomach distress
B.2.2.2c	
Non-chemically-mediated hazards	None

B.2.2.3	**Exposure assessment**
a) Rate and pattern of leachable substance release	No leachable substance
b) Physical form	No leachable substance
c) Estimate patient exposure (total or clinically available amounts)	No leachable substance

B.2.2.4	**Risk estimation**
a) Information on prior use of materials, additives, processing aids and other potential leachables	Polyester and Lycra fibre are widely used in manufacturing of similar devices and also in cloth industry
b) Data from biological evaluation	See analysis of SDS (Chapter 7.0) See OEKO-Tex certificates
c) Data from clinical tests and clinical experience	No serious incident or complaint reported.

	Refer to 820263 (A) - C8.2-8_v0.1 PMS - PSUR Report (MDR) and Knitted Socks_820284 (A) - STED118a Clinical Evaluation Report v0.1
d) Risk estimate from hazard identification and exposure assessment.	Low probability Low Severity

Risk evaluation and risk control for each identified hazard (B.2.2.5 - B.2.2.6)

Potential Hazard	Risk evaluation B.2.2.5	Risk Control B.2.2.6
Inhalation	Combustible dust not expected during normal or prolonged use Prosthetic socks is also worn inside a prosthetic socket No probability of occurrence	Not needed
Skin irritation from irritating substances	Low probability - Primary use is outside a prosthetic liner.	Yarns are OEKO-Tex100 certified to minimize the risk of irritating substances. Knitted Socks_820284 (A) - STED118a Clinical Evaluation Report v0.1 820263 (A) - C8.2-8_v0.1 PMS - PSUR Report (MDR)
Skin irritation from fiber particles and dusts	Continuous dust-generating rubbing may occur in a very loose prosthetic socket	Data collection from: Knitted Socks_820284 (A) - STED118a Clinical Evaluation Report v0.1 820263 (A) - C8.2-8_v0.1 PMS - PSUR Report (MDR)
Fire hazard	Not likely to happen under normal conditions of use	Not needed

B.2.3. Overall residual risk/benefit evaluation
Overall residual risk is considered to be acceptable. The benefit outweighs the risk.

B.2.4 Biological evaluation report
The evaluator considers the available data sufficient to confirm that the subject device has a low biological risk.

B.2.5 Post production information
Post production information is summarized in the 820263 (A) - C8.2-8_v0.1 PMS - PSUR Report (MDR).

9. Literature review

A literature review has been performed during the Clinical Evaluation. The relevant data available in literature are sufficient to demonstrate biological safety of the device under examination without the need to generate further data from actual testing.
See Knitted Socks_820284 (A) - STED118a Clinical Evaluation Report v0.1.

10. Evaluation

- Knitted socks are primarily used outside a prosthetic liner, not in direct contact with the skin. Contact with intact skin may occur if the patient will use the sock during rest time, while not wearing the prosthetic leg.
- Market experience. The device has been on the market for more than 12 years, with an approx. turnover of 500,000 units/year. No serious incident and no field safety corrective action has been reported on the subject device or on similar devices. See 820263 (A) - C8.2-8_v0.1 PMS - PSUR Report (MDR) and Knitted Socks_820284 (A) - STED118a Clinical Evaluation Report v0.1.
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- Risk/benefit profile is acceptable.

No further test is deemed to be necessary.

11. Conclusion

The biological risk of the device is considered to be low; the risk/benefit profile of the device is acceptable.
The existing non-clinical and clinical data, including history of safe use, meet the requirements of biological evaluation and therefore further animal testing would be unethical.