BIOLOGICAL EVALUATION REPORT

This plan prepared by

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For the Sponsor

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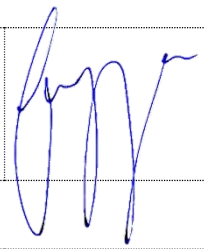
	Beyza SEYİTOĞLU MSc. Chemist	

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Approval (Reviewer from Sponsor)

CONTENT

1. INTRODUCTION

1.1 Scope and Purpose

This report has been prepared to address and evaluate the results of the Biological Evaluation process initiated on 01.10.2024 with BEP_2408035 according to EN ISO 10993-1 for the products which made of 100% cotton yarn woven fabric and in some cases accompanied by cotton or X-Ray yarn. Models were listed in BEP_2408035.

1.2 Definitions

Extract: Liquid that results from extraction of the test sample or control

Extractable substance: Substance that can be released from a medical device or material using either extraction solvents or extraction conditions, or both, that are expected to be at least as aggressive as the conditions of clinical use.

Leachable Substance: Substance that can be released from a medical device or material during clinical use.

1.3 Abbreviations, Symbols & Pictograms etc

PCD: Process Challenge Device

AET: Analytical Evaluation Threshold

MOS: Margin of Safety

CAS No: Chemical Abstracts Service Number

HS-GC-MS: Head Space Gas Chromatography

GC-MS: Gas Chromatography

LC-QTOF: Liquid chromatography coupled with quadrupole time-of-flight

ICP-MS: Inductively Coupled Plasma Mass Spectroscopy

ICP-OES: Inductively Coupled Plasma Optical Emission Spectroscopy

IC: Ion Chromatography

HQ: Highest Quantity

TQ: Total Quantity

VOC: Volatile Organic Compound

sVOC: semi-Volatile Organic Compound

nVOC: non-Volatile Organic Compound

NOAEL: No Observed Adverse Effect Level

LOAEL: Lowest Observed Adverse Effect Level

PDE: Permitted Daily Exposure

POD: Point of Departure

EED: Worst-case Estimated Exposure Dose

MoS: Magine of Safety

DRI: Dietary Reference Intakes

NS: Not Spesified

1.4 List of Tables, Figures, Pictures

2. TEST INFORMATION

2.1 Test Sample Identification

This report covers the biological evaluation of products consisting of cotton yarn fabric, cotton pads and X-Ray yarn with different size and shapes, the general model names of which are given below. Detailed information about the models is given in the BEP.

- NON-STERILE ABSORBENT GAUZE WITH / WITHOUT X-RAY
- NON-STERILE and STERILE ABSORBENT GAUZE COMPRESS WITH/WITHOUT X-RAY
- NON-STERILE and STERILE ABDOMINAL COMPRESS WITH/WITHOUT X-RAY
- NON-STERILE and STERILE SURGICAL COTTON PADS WITH/WITHOUT X-RAY

Information on the samples subject to testing is presented in the table below.

Table-2.1 Test Sample Information

Product Name (S-PCD):	20x20 cm 8 ply ABDOMINAL COMPRESS with COTTON PAD with X-RAY
Production Date / Lot:	04.10.2024 / 021024-175
Packaging Date / Lot:	04.10.2024 / 041024-172-219-01
EO Sterilization Date / Lot:	09.10.2024 / 521
Gamma Sterilization Date / Lot:	10.10.2024 / T1633.24

BER_2408035 Annex-2.1

BER_2408035 Annex-2.2

BER_2408035 Annex-2.3

BER_2408035 Annex-2.4

BER_2408035 Annex-2.5 KYFR26-3 Product Final Control Form

BER_2408035 Annex-2.6 Ethylene Oxide Sterilizer Result Form

BER_2408035 Annex-2.7 F932 Product Release Form - EO

BER_2408035 Annex-2.8 Gamma Certificate

2.2 Test Sample Preparation

The evaluation was made according to 10993-1, 10993-12 and 10993-18, taking into account the purpose of use of the device, duration of use and area of use, and the decision on how to prepare the medical device for testing was made as follows.

Table 2.2 Medical Device Definitions

Device Information	Description
Process Challenge Device	S-PCD 20x20 cm 8 ply Abdominal Compress with Cotton Pad with X-RAY
PCD Selection Justification	All product models consist of cotton yarn, cotton pad, and X-Ray yarn. However, each model contains different combinations of these components in varying amounts. Since a PCD containing all components simultaneously does not exist, it was decided to create a special PCD for testing before the testing process. This specially produced model will henceforth be referred to as S-PCD. S-PCD production was achieved by placing a cotton pad inside the existing abdominal compress product. Normally, the abdominal compress does not contain a cotton pad. During production, the abdominal compress and cotton components were weighed separately.

	There are 3 types of sterilization status for products before they are released to the market. Products can be marketed as non-sterile, EO sterile, or gamma sterile. The riskiest of these situations was considered to be the product that had been exposed to both EO and Gamma Sterilization. Therefore, S-PCD was sterilized repeatedly by being subjected to both sterilization processes. For a product with a stated shelf life of 5 years, it was deemed appropriate to conduct tests on a product that has reached the end of its shelf life after sterilization. However, since even accelerated stability studies for S-PCD take more than a year, it was decided to first conduct chemical characterization studies on the finished product. Once the accelerated stability studies are completed, the products will undergo another chemical characterization study, and this report will be updated with additional data. The maximum weight models determined for each age group and used in the calculations are as follows: Adult: 45x45 cm 16 ply ABDOMINAL COMPRESS - X-RAY / 108,9 g Children: 30x30 cm 8 ply ABDOMINAL COMPRESS - X-RAY / 23,1 g Infant: 20x20 cm 8 ply ABDOMINAL COMPRESS - X-RAY / 11,1 g	
Device part(s) with body contact (if applicable) (Acc.10993-1)	Tissue and Tissue Fluid	
	Externally communicating device – tissue/bone/dentine	
	When products are evaluated by considering 10993-1, it is seen that during the surgery, products get in to touch with inner body parts, organ surfaces and maybe some waste blood.	
Frequency and duration of body contact (Acc.10993-1)	Limited (<24h)	
Extraction conditions and methods (Acc.10993-12)	37±1 °C / 24±2 h	
Surface areas / Extract liquid volumes (Acc.10993-12)	Thickness: Irregularly shaped porous devices (low-density materials) Extraction ratio: 0,1 g/ml membranes, textiles	
Extraction Solvents (Acc.10993-18)	Polar	Water
	Semi-Polar:	Ethanol:Water (40:60)
	Non-Polar:	N/A (The device is not implantable. Therefore, there is no need to work with non-polar solvent.)

2.3 Test Laboratory Information

Tests are done according to the methods and test devices directed in 10993-18, with validated test methods. Detailed information about the equipment, consumables and chemicals used in the test is provided in the test report.

Table 2.3 Test Equipment Information

Extraction Preparation:	1 pcs : 22,6858 g / 226 mL water	
	1 pcs : 22,6847 g / 226 mL ethanol/water	
Test and Equipment	Organic Compounds, Volatile (VOC)	Thermo Fisher Scientific / ISQ 7000 GC-FID/MS
	Organic Compounds, Semi-volatile (SVOC)	Thermo Fisher Scientific / GC/MS Trace 1300
	Organic Compounds, Non-volatile (nVOC)	AB-Sciex 4600 QTOF
	Elemental Extractables,	Thermo Fisher Scientific ICP/MS ICAP-RQ Thermo Fisher Scientific ICP/OES ICAP 7400
	Anions	Thermo Scientific Dionex ICS-5000 Ion Chromatography

As a test laboratory selection criterion, it was expected that the Good Laboratory Practice Directive (2004/10/EC) accreditation requirement would be met in accordance with EU 2017/745, otherwise ISO 17025 accreditation requirement would be met by taking 10993-1 into account. As a result, it was decided to work with Yeditepe University R&D and Analysis Center Laboratories. The laboratory has also been accepted by many Ministries of Health regarding extractable/leachable tests in medicine.

BER_2408035 Annex-2.9 Yeditepe GLP Certificate

2.4 Test Reports Information

Detailed information about the equipment, consumables and chemicals used in the test is provided in the test report.

BER_2408035 Annex-2.10 Chemical Characterization Test Report – Abdominal Cotton Compress

3. ANALYSIS RESULTS

3.1 Chemical Characterization

3.1.1 Elemental Analysis

The results of elemental analyses performed with ICP-MS and ICP-OES are given below.

Table 3.1 ICP/MS Elemental analysis results

Element	Water				Ethanol/Water			
	1.injection	2.injection	3.injection	HQ	1.injection	2.injection	3.injection	HQ
	C (µg/mL)	**C (µg/mL)**	**C (µg/mL)**	**C (µg/mL)**	**C (µg/mL)**	**C (µg/mL)**	**C (µg/mL)**	**C (µg/mL)**
Li	0,004	0,004	0,004	0,004	<0,001	<0,001	<0,001	<LOD
Be	<0,001	<0,001	<0,001	<LOD	<0,001	<0,001	<0,001	<LOD
V	<0,001	<0,001	<0,001	<LOD	<0,001	<0,001	<0,001	<LOD
Cr	0,001	0,001	0,001	0,001	0,002	0,002	0,002	0,002
Mn	0,015	0,016	0,016	0,016	0,002	0,002	0,002	0,002
Co	<0,001	<0,001	<0,001	<LOD	<0,001	<0,001	<0,001	<LOD
Ni	0,004	0,003	0,004	0,004	0,002	0,002	0,002	0,002
Cu	0,004	0,003	0,004	0,004	0,001	0,001	0,001	0,001
As	<0,001	<0,001	<0,001	<LOD	<0,001	<0,001	<0,001	<LOD
Se	0,001	0,001	0,001	0,001	<0,001	<0,001	<0,001	<LOD
Sr	0,041	0,043	0,042	0,043	0,005	0,005	0,005	0,005
Mo	<0,001	<0,001	<0,001	<LOD	<0,001	<0,001	<0,001	<LOD
Ru	<0,001	<0,001	<0,001	<LOD	<0,001	<0,001	<0,001	<LOD
Rh	<0,001	<0,001	<0,001	<LOD	<0,001	<0,001	<0,001	<LOD
Pd	<0,001	<0,001	<0,001	<LOD	<0,001	<0,001	<0,001	<LOD
Cd	<0,001	<0,001	<0,001	<LOD	<0,001	<0,001	<0,001	<LOD
Sn	<0,001	<0,001	<0,001	<LOD	<0,001	<0,001	<0,001	<LOD
Sb	0,007	0,007	0,007	0,007	<0,001	<0,001	<0,001	<LOD
Ba	0,032	0,032	0,032	0,032	0,003	0,004	0,003	<LOD
Os	<0,001	<0,001	<0,001	<LOD	<0,001	<0,001	<0,001	<LOD
Ir	<0,001	<0,001	<0,001	<LOD	<0,001	<0,001	<0,001	<LOD
Pt	<0,001	<0,001	<0,001	<LOD	<0,001	<0,001	<0,001	<LOD
Au	<0,001	<0,001	<0,001	<LOD	<0,001	<0,001	<0,001	<LOD
Hg	<0,001	<0,001	<0,001	<LOD	<0,001	<0,001	<0,001	<LOD
Tl	<0,001	<0,001	<0,001	<LOD	<0,001	<0,001	<0,001	<LOD
Pb	<0,001	<0,001	<0,001	<LOD	0,002	0,002	0,002	<LOD
Ti	0,001	0,001	0,001	0,001	<0,001	<0,001	<0,001	<LOD
Ag	<0,001	<0,001	<0,001	<LOD	<0,001	<0,001	<0,001	<LOD
Ca	5,26	5,37	5,32	5,37	0,61	0,61	0,61	0,61
K	1,76	1,82	1,78	1,82	0,18	0,18	0,18	0,18
Na	15	15,12	15	15,12	2,34	2,35	2,34	2,35
Mg	3,24	3,26	3,25	3,26	0,56	0,56	0,56	0,56
Fe	<0,05	<0,05	<0,05	<LOD	<0,05	<0,05	<0,05	<LOD
Al	0,05	0,06	0,05	0,06	0,1	0,1	0,1	0,10
Si	1,12	1,13	1,14	1,14	0,16	0,15	0,15	0,16
Zn	<0,05	<0,05	<0,05	<LOD	<0,05	<0,05	<0,05	<LOD

3.1.2 Ion Analysis

The results of anion analyses performed with IC are given below.

Table 3.2 Results of Anion Analysis by IC

Anion	Extract Medium	1.injection	2.injection	3.injection	HQ
		C (µg/mL)	C (µg/mL)	C (µg/mL)	C (µg/mL)
F^-	Water	1,33	1,38	1,37	1,38
	Ethanol/Water	1,08	1,08	1,17	---
Cl^-	Water	3,13	3,10	3,11	---
	Ethanol/Water	3,40	3,39	3,41	3,41
NO_2^-	Water	<LOD	<LOD	<LOD	---
	Ethanol/Water	<LOD	<LOD	<LOD	---
SO_4^{2-}	Water	8,57	8,41	8,33	8,57
	Ethanol/Water	3,36	4,03	4,02	---
NO_3^-	Water	<LOD	<LOD	<LOD	---
	Ethanol/Water	<LOD	<LOD	<LOD	---
PO_4^{3-}	Water	3,33	3,41	3,40	3,41
	Ethanol/Water	2,64	2,05	2,08	---
Br^-	Water	<LOD	<LOD	<LOD	---
	Ethanol/Water	<LOD	<LOD	<LOD	---

3.1.3 VOC Analysis

No extractable/leachable compounds were detected in the HS-GC/MS Volatile Organic Compound analyses.

Table 3.3 Results of VOC by HS-GC-MS

VOC	CAS RN	Extract Medium	1.injection	2.injection	3.injection	HQ
			C (µg/mL)	C (µg/mL)	C (µg/mL)	(µg/mL)
---	---	Water	---	---	---	---
		Ethanol/Water	---	---	---	---

3.1.4 sVOC Analysis

The results of sVOC analyses performed with GC-MS are given below.

Table 3.4 Results of sVOC by GC-MS

sVOC	CAS RN	Extract Medium	1.injection	2.injection	3.injection	HQ
			C (µg/mL)	C (µg/mL)	C (µg/mL)	(µg/mL)
Caprolactam	105-60-2	Water	---	---	---	---
		Ethanol/Water	1,59	1,50	1,82	1,82

3.1.5 nVOC Analysis

The results of nVOC analyses performed with LC-QTOF are given below.

Table 3.5 Results of nVOC by LC/QTOF

nVOC	CAS RN	Extract Medium	Screening	1.injection	2.injection	3.injection	HQ
				C (µg/mL)	C (µg/mL)	C (µg/mL)	(µg/mL)
Dexpanthenol	81-13-0	Water	Pozitive	1,33	1,31	1,59	1,59
Lauric acid diethanolamide	120-40-1	Water	Pozitive	0,31	0,24	0,32	0,32
PEG9-CH3 H NH4	6048-68-6	Water	Pozitive	0,16	0,15	0,17	0,17

4. TOXICOLOGICAL ASSESMENT

4.1 Toxicological Data's

The medical devices subject to evaluation were created as follows, taking into account 10993-1 and 17.

Table 4.1 Medical Device Specific Information

Device Information	Description
Device Name	• Non-Sterile Absorbent Gauze Wıth / Without X-Ray • Non-Sterile and Sterile Absorbent Gauze Compress With/Without X-Ray • Non-Sterile and Sterile Abdominal Compress With/Without X-Ray • Non-Sterile and Sterile Surgical Cotton Pads With/Without X-Ray
Device part(s) with body contact	Tissue and Tissue Fluid
(if applicable)	Direct Contact
Number or quantity of devices contacting body	2 pcs / surgery (exaggerated condition maybe 10 pcs / lifetime)
	It was anticipated that the device would be used 2 times per surgery. However, considering the possibility of repeated operations, errors, and multiple manipulations at the same time, this number has been agitated and accepted as 10. Since the purpose of the device is to absorb bleeding, it has been accepted that a device can be in contact with the relevant tissue for a maximum of 1 hour during a surgery, after which it will reach its maximum capacity and be replaced.
Frequency and duration of body contact	≤1d (Acc.MoS / 10993-17)
	Limited (<24h) (Acc.10993-1)
Individual(s) exposed to the device	men (70kg), women (>60 kg or lower), children (>1 year to ≤16 years of age; 10 kg), infants (<1 year; 3,5 kg)

For evaluation of toxicological data, the toxicological information summarized according to ISO 10993-17 below.

Table 4.2 TSL Information

	Constituent Name	CAS RN	Classification ****			HQ	TQ (µg/device)		**Is constituent excluded from TSL?	Is TQ less than TSL ≤30 d? (120 µg)	
			1	2	3	(µg/mL)	S-PCD	MAX*		S-PCD	MAX*
METALS*	Li	7439-93-2		3		0,004	0,907	4,356	No	Yes	Yes
	Cr	7440-47-3		3		0,002	0,454	2,178	No	Yes	Yes
	Mn	7439-96-5		Other		0,016	3,630	17,424	No	Yes	Yes
	Ni	7440-02-0		2A		0,004	0,907	4,356	No	Yes	Yes
	Cu	7440-50-8		3		0,004	0,907	4,356	No	Yes	Yes
	Se	7782-49-2		2B		0,001	0,227	1,089	No	Yes	Yes
	Sr	7440-24-6		N/A		0,043	9,755	46,827	No	Yes	Yes
	Sb	7440-36-0		3		0,007	1,588	7,623	No	Yes	Yes
	Ba	7440-39-3		3		0,032	7,259	34,848	No	Yes	Yes
	Pb	7439-92-1		**1**		0,002	0,454	2,178	**YES**	Yes	Yes
	Ti	7440-32-6		N/A		0,001	0,227	1,089	No	Yes	Yes
	Ca	7440-70-2		Other		0,61	138,383	664,290	No	**No**	**No**
	K	7440-09-07		Other		1,82	412,882	1.981,980	No	**No**	**No**
	Na	7440-23-5		Other		15,12	3.430,093	16.465,680	No	**No**	**No**
	Mg	7439-95-4		Other		3,26	739,557	3.550,140	No	**No**	**No**
	Al	7429-90-5		Other		0,1	22,686	108,900	No	Yes	Yes
	Si	7440-21-3		N/A		0,16	36,297	174,240	No	Yes	**No**
ANIONS	F^-	16984-48-8		N/A		1,38	313,064	1.502,820	No	**No**	**No**
	Cl^-	16887-00-6		N/A		3,41	773,586	3.713,490	No	**No**	**No**
	SO_4^{2-}	14808-79-8		N/A		8,57	1.944,173	9.332,730	No	**No**	**No**

	PO_4^{3-}	14265-44-2	N/A			3,41	773,586	3.713,490	No	**No**	**No**
ORGANICS	VOC	---	---	---	---		---	---	---	---	---
	sVOC	105-60-2	---	**3**	4	1,820	412,882	1.981,980	**YES**	**No**	**No**
	nVOC	81-13-0	---	**3**	---	1,590	360,704	1.731,510	**YES**	**No**	**No**
		120-40-1	---	**3**	---	0,320	72,595	348,480	**YES**	Yes	**No**
		6048-68-6	---	---	---	0,170	38,566	185,130	No	Yes	**No**

**CAS number information is given for the elements, taking into account their metallic states.*

**YES means constituent is a cohort of concern or excluded chemical. No means constituent is not a cohort of concern or excluded chemical.

****For all ions, data for Na salts were taken into account and CAS numbers were given accordingly.*

**** For all VOCs "1-ICH Class, 2-Cramer Class, 3-CLP Category is given. For metals ICH class is given.

****Structures with Cramer values of III will henceforth be considered as CoCs.

All extractable/leachable chemical structures detected are correctly and clearly defined, and CAS numbers are shared in the table. Therefore, there is no need to apply the Safety Concern Threshold. Instead, the defined exposure values for each chemical were found in the ECHA database and calculations were made one by one.

Table 4.3 Constituent Specific Toxicological İnformation

Compound	CAS No	Test Species	Exposure Determinants			Toxicological Information				Information Source for PDE	PDE Value µg/day
			Route / Method	Vehicle	Frequency / Duration	Type of harm Reported	Type of POD	Information Source for POD	POD value		
Li	7439-93-2	N/A	Parenteral	N/A	N/A	N/A	N/A	N/A	N/A	ICH Q3D (R2)	250
Cr	7440-47-3	N/A	Parenteral	N/A	N/A	N/A	N/A	N/A	N/A	ICH Q3D (R2)	1.100
Mn	7439-96-5	Rat	Oral	Drinking water	NS	Neurotoxicity	LOAEL	WHO /EFSA	25 mg/kg bw day	NCBI (DRI)	2.000
Ni	7440-02-0	N/A	Parenteral	N/A	N/A	N/A	N/A	N/A	N/A	ICH Q3D (R2)	20
Cu	7440-50-8	N/A	Parenteral	N/A	N/A	N/A	N/A	N/A	N/A	ICH Q3D (R2)	300
Se	7782-49-2	N/A	Parenteral	N/A	N/A	N/A	N/A	N/A	N/A	ICH Q3D (R2)	80
Sr	7440-24-6	Rat	Oral	NS	NS	Repeated dose toxicity	NOAEL	ECHA CHEM	9.9 mg/kg bw/day	TSL	120
Sb	7440-36-0	N/A	Parenteral	N/A	N/A	N/A	N/A	N/A	N/A	ICH Q3D (R2)	90
Ba	7440-39-3	N/A	Parenteral	N/A	N/A	N/A	N/A	N/A	N/A	ICH Q3D (R2)	700
Pb	7439-92-1	N/A	Parenteral	N/A	N/A	N/A	N/A	N/A	N/A	ICH Q3D (R2)	5
TiO2	13463-67-7*	N/A	Oral	N/A	N/A	N/A	N/A	N/A	N/A	ICH Q3D (R2)	25.000
CaCl2	10035-04-8*	Human (Infants 3 to 9 months)	Oral	NS	NS	Excretion	NOAEL	FDA GRASS	1750 mg/day	Pubchem/NCBI (DRI)	1.500.000
KCl	7447-40-7*	Rat (M)	Oral	Feed	2 years	Repeated dose toxicity	NOAEL	ECHA	1820 mg/kg bw/day	FDA (DRI)	2.300.000
NaCl	7647-14-5*	Rat	Oral	Feed	2 years (Chronic)	Repeated dose toxicity	LOAEL	ECHA / ECHA CHEM	2533 mg/kg bw/day	EFSA	2.000.000
Mg	7439-95-4	Rat	Oral	NS	Sub-chronic to chronic	repeated dose toxicity	NOAEL	ECHA CHEM	250 mg/kg bw/day	EFSA	250.000
AlCl3	7446-70-0*	Rats (Wistar)	Oral	Drinking water	30, 60, or 90 days	Chronic / Repeated Dose Toxicity	NOAEL	EFSA	30 mg Al/kg bw/day	WHO	2.000
Na2SiO3	6834-92-0*	Rat (Wistar)	Oral	Water	daily / 3 months	repeated dose toxicity	NOAEL	OECD	227 mg/kg bw/day	OECD	20.000
F^-	16984-48-8*	Human	Oral	Water	NS	Endpoint Value	NOAEL	PubChem	0.1 mg/kg bw/day	EFSA	7.000
Cl^- (NaCl)	16887-00-6*	Rat	Oral	Feed	2 years (Chronic)	Repeated dose toxicity	LOAEL	ECHA / ECHA CHEM	2533 mg/kg bw/day	EFSA	2.000.000
SO_4^{2-} (Na2SO4)	7757-82-6*	Rat (M)	Oral / Feed	Feed	Daily, 44 weeks	Repeated dose toxicity	NOAEL	OECD	320 mg/kg/day	EFSA	600.000
PO_4^{3-}	14265-44-2*	Rat	Intravenous	NS	Daily / 14 days	Nephrotoxicity (proteinuria)	NOAEL	PubChem	28 mg/kg bw/day	NIH	3.000.000
Caprolactam	105-60-2	Rat	Oral	Feed	103 weeks	Chronic / Repeated Dose Toxicity	LOAEL	EPA	125 mg/kg/day	TSL	120
Dexpanthenol	81-13-0	Rat	Oral/Gavage	Water	Daily / 90 days	Subchronic / Repeated dose toxicity	NOAEL	ECHA CHEM	1000 mg/kg bw/day	TSL	120
Lauric acid diethanolamide	120-40-1	Rat	Dermal	Not Specified	Long term exposure	Repeated dose toxicity	NOAEL	ECHA CHEM	50 mg/kg bw/day	TSL	120
Tetraethylene glycol monomethyl ether	23783-42-8	Rat	Oral	Water	36 days (M) 53-65 days (F)	Repeated dose toxicity	NOAEL	ECHA CHEM	1000 mg/kg bw/day	TSl	120

**The TiO2 value from ICH was used for Ti. Data on the water-soluble forms of metals and ions were also obtained.*

***For chemicals for which no accessible data source is available, the TSL limit value (120 µg/day) has been taken as PDE Value 120 µg/day.*

Due to the absence of substance-specific toxicological data for CAS 6048-68-6 (nonaethylene glycol monomethyl ether), a read-across approach was applied in accordance with the principles described in ISO 10993-17 and established OECD read-across frameworks, and toxicological data from the closely related analogue octaethylene glycol monomethyl ether (CAS 23783-42-8) were used for hazard characterization and derivation of health-based exposure limits. This analogue was selected because it belongs to the same homologous series of methoxy-terminated polyethylene glycol monoethers and differs only by a single ethylene oxide repeat unit (n=8

versus n=9), resulting in nearly identical chemical structure, physicochemical properties, and expected biological behavior. Both substances share the same methoxy terminal group and linear polyethylene oxide backbone with repeating –CH_2CH_2O– units, and no additional functional groups or structural alerts are present that would modify toxicity. Estimated molecular fingerprint similarity values consistently exceed the commonly accepted threshold for high-confidence read-across, with predicted Tanimoto (ECFP4) similarity in the range of approximately 0.93–0.97, atom-pair similarity approximately 0.92–0.96, and MACCS key similarity above 0.95. Comparable high similarity values are also obtained for adjacent homologues such as decaethylene glycol monomethyl ether (PEG-10 methyl ether), with predicted Tanimoto similarity values of approximately 0.94–0.98, and for methoxy polyethylene glycol grades with average chain lengths between approximately 7 and 12 ethylene oxide units, where QSAR fingerprint similarity values typically fall between 0.90 and 0.98. These results demonstrate that CAS 6048-68-6 and CAS 23783-42-8 belong to a well-defined homologous PEG monoether category characterized by identical functional groups, equivalent linear polyethylene oxide backbones, minimal molecular weight differences, and the same expected metabolic fate. Similarity values in the range of approximately 0.95–0.98 are generally considered indicative of very high structural equivalence in regulatory toxicology and are consistent with category-based read-across approaches accepted under OECD, REACH, and ISO 10993 biological evaluation principles, so it was used as the primary analog substance for the toxicological evaluation of CAS 6048-68-6 instead of CAS 23783-42-8.

4.2 Application of Analytical Evaluation Threshold

The analytical threshold has been applied for metals with known PDE values and organic structures that can be identified, which termed the AET. For this, the prerequisite that the detected amounts are higher than the LOD and LOQ values has also been taken into account. The extract processing has been considered during analytical concentration calculations and the calculation of the AET value (Formula-1) adjusted accordingly.

$$AET = \frac{DBT \times \frac{A}{B \times C}}{UF}$$ Formula-1

Table-4.4 Summary of AET Evaluation

Constituent Name	CAS RN	DBT (PDE)*	A	B	C	UF	AET	HQ	HQ > AET?
		(µg/day)	(device)	(mL)	(device/day)		(µg/mL)	(µg/mL)	
Li	7439-93-2	250	1,00	226	2	2	0,277	0,004	No
Cr	7440-47-3	1.100	1,00	226	2	2	1,217	0,002	No
Mn	7439-96-5	2.000	1,00	226	2	2	2,212	0,016	No
Ni	7440-02-0	20	1,00	226	2	2	0,022	0,004	No
Cu	7440-50-8	300	1,00	226	2	2	0,332	0,004	No
Se	7782-49-2	80	1,00	226	2	2	0,088	0,001	No
Sr	7440-24-6	120	1,00	226	2	2	0,133	0,043	No
Sb	7440-36-0	90	1,00	226	2	2	0,100	0,007	No
Ba	7440-39-3	700	1,00	226	2	2	0,774	0,032	No
Pb	7439-92-1	5	1,00	226	2	2	0,006	0,002	No
TiO2	13463-67-7*	25.000	1,00	226	2	2	27,655	0,001	No
CaCl2	10035-04-8*	1.500.000	1,00	226	2	2	1.659,292	0,61	No
KCl	7447-40-7*	2.300.000	1,00	226	2	2	2.544,248	1,82	No
NaCl	7647-14-5*	2.000.000	1,00	226	2	2	2.212,389	15,12	No
Mg	7439-95-4	250.000	1,00	226	2	2	276,549	3,26	No
AlCl3	7446-70-0*	2.000	1,00	226	2	2	2,212	0,1	No
Na2SiO3	6834-92-0*	20.000	1,00	226	2	2	22,124	0,16	No
F^-	16984-48-8	7.000	1,00	226	2	2	7,743	1,38	No
Cl^- (NaCl)	16887-00-6	2.000.000	1,00	226	2	2	2.212,389	3,41	No
SO_4^{2-} (Na2SO4)	7757-82-6	600.000	1,00	226	2	2	663,717	8,57	No
PO_4^{3-}	14265-44-2	3.000.000	1,00	226	2	2	3.318,584	3,41	No
Caprolactam	105-60-2	120	1,00	226	2	2	0,133	1,82	**Yes**
Dexpanthenol	81-13-0	120	1,00	226	2	2	0,133	1,59	**Yes**
Lauric acid diethanolamide	120-40-1	120	1,00	226	2	2	0,133	0,32	**Yes**
Tetraethylene glycol monomethyl ether	23783-42-8	120	1,00	226	2	2	0,133	0,17	**Yes**

*These values were used for components where the PDE value is directly available. For those where the PDE value is not available, the TTC value of 120 µg/day was considered.

***According to literature data, although the RSD factor is below 10% (-MS, like device etc.) analyses, UF is taken as 2, which is the highest possible figure for this type of analysis.*

For metals and iyons, extractables/leachables concentrations are below the AET quantified as a prerequisite for their toxicological risk assessment. Therefore, it has been determined that the extractable substances are not toxic due to their metal and ion content.

Table-4.5 Threshold of Toxicological Concern Information

Constituent Name	CAS RN	HQ (µg/mL)	TQ (µg/device)		Is constituent Excluded from TTC?	Is the quantity less than TTC?	
			S-PCD	MAX* (Adult)		S-PCD	MAX* (Adult)
Caprolactam	105-60-2	1,820	412,882	1.981,980	**YES**	**No**	**No**
Dexpanthenol	81-13-0	1,590	360,704	1.731,510	**YES**	**No**	**No**
Lauric acid diethanolamide	120-40-1	0,320	72,595	348,480	**YES**	Yes	**No**
Tetraethylene glycol monomethyl ether	23783-42-8	0,170	38,566	185,130	No	Yes	**No**

*Extrapolated with calculation.

Given that the quantities of the detected organic structures are above the TTC level and some cannot be included in the TTC assessment, the MoS assessment will continue.

4.3 Application of Margine of Safety

Exposure dose estimation based on release kinetics information shall be applied to identified constituents using a reference standard suitable for accurate quantification and targeted chemical analysis. The medical device is categorized as limited contact with the body, the exposure dose shall be calculated using Formula-2.

$$EED_{max} = \frac{HQ \times SF}{BW_l} \quad \text{Formula-2}$$

The modifying factor shall be calculated as the product of all uncertainty factors as shown in Formula-3. The UF_n values given below will be used in this formulation.

$$MF = UF_{(Tl)1} \times UF_{(Tl)2} \times UF_{(Tl)n} \quad \text{Formula-3}$$

UF1: 10 (Uncertainty for intraspecies variation)
UF2: 10 (Uncertainty for interspecies differences)
UF3: 1 (Route-to-route)
UF4: 1 (Exposure duration)
UF5: 3 (NOAEL)
UF5: 10 (LOAEL)

After the POD (NOAEL, LOAEL, etc.) and the modifying factor are determined, the TI shall be calculated in amount (mg or µg) per kilogram body mass per day, as shown in Formula-4.

$$Tl = \frac{POD}{MF} \quad \text{Formula-4}$$

Calculation of margin of safety depends on the following Formula-5.

$$MoS = \frac{Tl \text{ or } TCL}{EED_{max}} \quad \text{Formula-5}$$

Table-4.6 Tolerable Contact Level and Tolerable Intake İnformation

Constituent Name	CAS RN	Harm	Type of POD	POD (µg/kg-bw day)	UF1	UF2	UF3	UF4	UF5	MF	TI (µg/kg-day)
Caprolactam	105-60-2	Chronic / Repeated Dose Toxicity	LOAEL	125.000	10	10	1	1	10	1000	125,00
Dexpanthenol	81-13-0	Subchronic / Repeated dose toxicity	NOAEL	1.000.000	10	10	1	1	3	300	3.333,33
Lauric acid diethanolamide	120-40-1	Repeated dose toxicity	NOAEL	50.000	10	10	1	1	3	300	166,67
Tetraethylene glycol monomethyl ether	23783-42-8	Reproductive toxicity (reduced epididymal sperm density)	NOAEL	1.000.000	10	10	1	1	3	300	3.333,33

**Extrapolated with calculation.*

Table-4.7 Estimated Exposure Dose

Constituent Name	CAS RN	HQ (µg/mL)	TQ (µg/device)				SF	BWL			Rd	EED_{max} (2 to 30 d)			
			S-PCD	MAX* (Adult)	MAX* (Children)	MAX* (Infant)		Adult (f/m)	Children	Infant		S-PCD	MAX* (Adult)	MAX* (Children)	MAX* (Infant)
Caprolactam	105-60-2	1,82	412,88	1.981,98	420,42	202,02	2	60	10	3,5	2	6,88	33,03	42,04	57,72
Dexpanthenol	81-13-0	1,59	360,70	1.731,51	367,29	176,49	2	60	10	3,5	2	6,01	28,86	36,73	50,43
Lauric acid diethanolamide	120-40-1	0,32	72,59	348,48	73,92	35,52	2	60	10	3,5	2	1,21	5,81	7,39	10,15
Tetraethylene glycol monomethyl ether	23783-42-8	0,17	38,57	185,13	39,27	18,87	2	60	10	3,5	2	0,64	3,09	3,93	5,39

**Extrapolated with calculation.*

Table-4.8 Summary of Margine of the Safety Evaluation

Constituent Name	CAS RN	TI	EEDmax (≤1 d)				MoS	Acceptable?		Acceptable?		Acceptable?
			S-PCD	MAX* (Adult)	MAX* (Children)	MAX* (Infant)	Adult (f/m)		Children		Infant	
Caprolactam	105-60-2	125,00	6,88	33,03	42,04	57,72	3,78	Yes	2,97	Yes	2,17	Yes
Dexpanthenol	81-13-0	3.333,33	6,01	28,86	36,73	50,43	115,51	Yes	90,75	Yes	66,10	Yes
Lauric acid diethanolamide	120-40-1	166,67	1,21	5,81	7,39	10,15	28,70	Yes	22,55	Yes	16,42	Yes
Tetraethylene glycol monomethyl ether	23783-42-8	3.333,33	0,64	3,09	3,93	5,39	1080,32	Yes	848,82	Yes	618,27	Yes

**Extrapolated with calculation.*

5. TOXICOLOGICAL EVALUATION

Data on extractable/leachable chemicals obtained during Chemical Characterization studies are summarized in article 3. Toxicological evaluations were made based on these data in Article 4.

First, all analytes detected in the extractable/leachable results were classified, and those excluded from the CoC were evaluated using the TSL. Detections below this limit were deemed safe and therefore not proceeded to further evaluation. Subsequently, for analytes other than CoC, an AET assessment was conducted, and those below the limits were deemed safe and therefore not proceeded to further evaluation. Finally, MoS evaluation was performed for all remaining notable analytes. The PCD models and weights detailed in Table 4.1 were used in the calculations. This was also seen in the MoS assessment results. The products are toxicologically safe for use.

6. RISK ASSESMENT

Cotton abdominal compresses have been produced using technologically advanced methods for centuries. While the processing of cotton, the main raw material, has improved over time, it hasn't changed significantly. Since the purpose of these devices is to absorb and remove blood that needs to be extruded during surgery, cotton has maintained its position as the safest material for this purpose for years and continues to do so today. Therefore, the primary aim of this study was not to determine the suitability of cotton and cotton yarn for the device, but rather to consider the potential toxicological effects of possible agents and residues/contaminants in the applied processes on the patient. This has also been observed in extractable/leachable studies, where materials that leach from the products naturally become process waste. Of course, since washing processes are also included in the processes, it has been shown that these wastes are safely disposed of in extractable/leachable studies with results in the ppb range.

Furthermore, considering the use of the products, and taking into account that the absorbed blood or extruded material is not actually returned to the body but is retained by the device, it is also seen that there is no possibility of the existing extractable/leachable analytes dissolving in the blood and re-entering the bloodstream. Therefore, it is observed that the risks that are exaggerated and amplified do not actually exist or are acceptable.

Studies conducted in light of these assessments have sufficiently revealed the existing toxicological risks and demonstrated that safety limits are being applied.

Therefore, further evaluation and evidence generation were not deemed necessary. The products are safe for patient use, considering their defined intended medical device uses.

7. ENDPOINTS of BIOLOGICAL EVALUATION

As planned in the BEP, since the chemical characterization study proves the safety of the device, an additional biocompatibility endpoint study is not required. Therefore, no study has been conducted that progresses towards animal testing, and animal welfare has also been ensured.

The products have been on the market for a long time, and no complaints or reports regarding any of the defined biocompatibility requirements have been received. No human data have been observed in post-marketing clinical surveillance data. In addition, data from previous biocompatibility tests are summarized below.

Report Number	Test Information	Test Condition	Result	Annex
24.08.2017 2017-IVV-SEN-079-388 Kırıkkale University (KÜBTUAM)	Sensitization ISO 10993-10	intradermal induction phase on guinea pigs	Score:0 Acceptable	BER_2408035 Annex-7.1
24.08.2017 2017-IVV-IRT-079-379 Kırıkkale University (KÜBTUAM)	Irritation ISO 10993-10	4-hour patch test in rabbits	Score:0 Negligible	BER_2408035 Annex-7.2
07.08.2017 2017-IVT-KİE-070-348 Kırıkkale University (KÜBTUAM)	Haemolytic effect ISO 10993-4 ASTM F756	Interaction with blood in EDTA tubes for 15-90 minute periods; haemolysis test	Score: 0,243-0,311-0,473-0,493 (15m, 30m, 45m, 90m) No haemolytic effect	BER_2408035 Annex-7.3
07.08.2017 2017-IVT-SİT-070-352 Kırıkkale University (KÜBTUAM)	Cytotoxicity ISO 10993-5:2009	MTT test per ISO 10993-5; L929 Fibroblast cells and 72-hour extract at 37°C.	Score: %95,36 No cytotoxic effect	BER_2408035 Annex-7.4
29.06.2016 2016-BUL-SİT-043-203 Kırıkkale University (KÜBTUAM)	Cytotoxicity ISO 10993-5:2009	MTT test per ISO 10993-5; L929 Fibroblast cells and 72-hour extract at 37°C	Score: %89.17 No cytotoxic effect	BER_2408035 Annex-7.5
19.09.2016 ARGEDS-2016/29 Hacettepe University	Sensitization ISO 10993-10	Preparation per ISO 10993-12; direct contact method on guinea pigs	Score:0 Does not cause sensitization	BER_2408035 Annex-7.6
22.06.2016 ARGEDS-2016/29 Hacettepe University	Irritation ISO 10993-10	Saline and sunflower oil extracts per ISO 10993-12; intradermal injection in rabbits	Score:0,06 Does not cause intradermal irritation	BER_2408035 Annex-7.7
22.06.2016 ARGEDS-2016/29 Hacettepe University	Hemolytic effect ISO 10993-4 ASTM F756	Solid sample extract per ISO 10993-12 (72 hours at 37°C in saline solution)	Score: % 0.09	BER_2408035 Annex-7.8
12.12.2006 Hacettepe University	EN ISO 10993-5	Extract test (contact of cells with original extract).	PASS Sample found non-cytotoxic	BER_2408035 Annex-7.9
12.12.2006 Hacettepe University	EN ISO 10993-10	Irritation test on non-sterile gauze bandage sample.	PASS Sample does not cause irritation	BER_2408035 Annex-7.10
12.12.2006 Hacettepe University	EN ISO 10993-10	Sensitization test on non-sterile gauze bandage sample.	PASS Sample does not cause sensitization	BER_2408035 Annex-7.11

8. TECHNICAL EXPERT RESUME

Beyza SEYİTOĞLU

02.11.1979, ANTALYA, TURKEY

MSc Chemist

Senior Professional with over 20 years of multinational expertise of regulatory affairs, quality assurance and quality control in the medical devices and pharmaceutical industries. +2000 man/days of on-site audit and technical file review experience at the end of the 9 year work period as Lead Auditor in Notified Body.

2020 - Still M.Sc., Pharmaceutical Toxicology
Yeditepe University, Faculty of Pharmacy, Istanbul
2006-2008 M.Sc., Nuclear Applications Department
Ege University, Institute of Nuclear Sciences, Izmir
1999-2004 B.Sc., Chemistry
Gazi University, Faculty of Science-Literature, Ankara

Oct 2020 - Still EUMED Consulting Co. Ltd., Istanbul
Owner & CEO Field Of Activity: Regulatory Consultancy Activities for companies in medical device sector, Non-Governmental Organisation (MASSIAD and ISEK) cooperation activities

Oct 2020 – March 2021 TST RAKOR Medical Devices Industry and Trade Inc., Istanbul
Regulatory Affairs Manager
Project Based Field Of Activity: Production of Orthopaedic Implants; Hip Joint Implants, Hip Replacements, Knee Replacements, Plates, Nails, Medical Hand Tools

June 2016- Sep 2020 KİWA Certification Services Co., Istanbul (NOTIFIED BODY 1984)
Lead Auditor
Technical Expert Field Of Activity: System and Product Certification Service, Conformity Assessment

Lead Auditor at; ISO 13485, ISO 9001
Technical Expert at; Codes; MD 0101, MD 0102, MD 0104, MD 0106, MD 0108, MD 0301, MD 1401 (isotope radiation), MDS 7006 (EO & Gama& Steam & Aseptic)

Oct 2014- April 2016 KANSUK Laboratory Inc., Istanbul
Quality Control Manager
Field Of Activity: Production of Blood Bag Sets, Leukocyte Filter and Blood Collection Sets and Pharmaceutics (glycerine suppository, skin and mucosa antiseptic disinfectant, vaginal suppository for antiseptic disinfectant, pastille for oral antiseptic antiviral, oral powder for laxatives and acidity for stoma, oral rehydration salt, laxatives), Parenteral solutions (Isotonic serum solutions, dextrose solutions, ringer solutions, peritoneum dialysis solutions)

June 2014- April 2016 MEDİKOKİM Medical Products Ltd. Istanbul (part time)
Quality Responsible
Field of Activity: Neurosurgical brain pad, surgical pads, Wound care products; supporting bands, supportive bands, protective bands,

April 2012- April 2014 KİWA Certification Services Co., Istanbul (NOTIFIED BODY 1984)
Medical Program Responsible Field Of Activity: System and Product Certification Service, Conformity Assessment
Lead Auditor at; ISO 13485, ISO 9001

Technical Expert at; Codes; MD 0101, MD 0102, MD 0104, MD 0106, MD 0108,MDS 7006 (EO & Gama& Steam & Aseptic)

April 2011 – March 2012 DELTA Cosmetic Co., Istanbul
Quality Assurance Manager & QMR Field of Activity: Personal care (shampoo, conditioner, body lotion, lotion, baby products, etc.), cleaning products (mouthwash, hand soap, hand sanitizer, etc.) &household products (surface cleaners, air freshener)

Jan 2009 - Dec 2010 MOLTEK Molecular Technologies Co., Istanbul
Quality Control Responsible Field of Activity: Radiopharmaceutical Manufacturing (18F-FDG)

Sep 2006 – July 2008 Ege University, Institute of Nuclear Sciences, Izmir
R&D Project Assistant Field of Activity: Research and Development of Radiopharmaceuticals

April 2004 – June 2006 PLAS-SET Medical Technical Materials Co, Istanbul
Quality Control Expert Field of Activity: Production of Chemical IVD kit, plastic injection ve blood tube, cleaning & disinfectant chemicals

2009, B. Seyitoglu, F. Yurt Lambrecht, Durkan - Labeling of Apigenin with 131I and bioactivity of 131I-apigenin in male and female rats, J. Radioanalytical and Nuclear Chemistry, 279,3, 867-873, 2009.

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9. REVISION HISTORY

28.02.2026	00	First Issue

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OECD https://www.echemportal.org

ECHA CHEM https://chem.echa.europa.eu/

EPA https://www.epa.gov/iris

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