Consultancy :: Training :: Support :: Auditing

Nelson Labs Open House "2020 The Year of Change"

Leuven, 4th – 5th March 2020

Henry Sibun

Changes to ISO 10993-1 and relationship to Medical Devices Regulation

Introduction:

- **TÜV SÜD Product Service GmbH**
  - Based in Munich and the largest medical device notified body
- **Henry Sibun** BSc (Tech) Hons, CQI CQP, MRSB CBiol
  - Biologist with work experience in the water, food & medical devices industries in quality/regulatory/microbiology roles
  - **27** years: medical device industry
  - **22** years: Notified Body Lead Auditor and Technical Reviewer for TÜV SÜD Product Service GmbH
  - **9+** years: consultant to medical device/pharma industries
- **Thank you to Dr Christina Reufsteck** at TÜV SÜD Product Service GmbH for input to some of the slides

Contents

Changes to ISO 10993-1 and relationship to Medical Devices Regulation (EU) 2017/745

1) Introduction
2) Change in approach MDD → MDR
3) MDR change overview
4) Key ISO 10993-1:2018 changes
5) Summary and conclusion

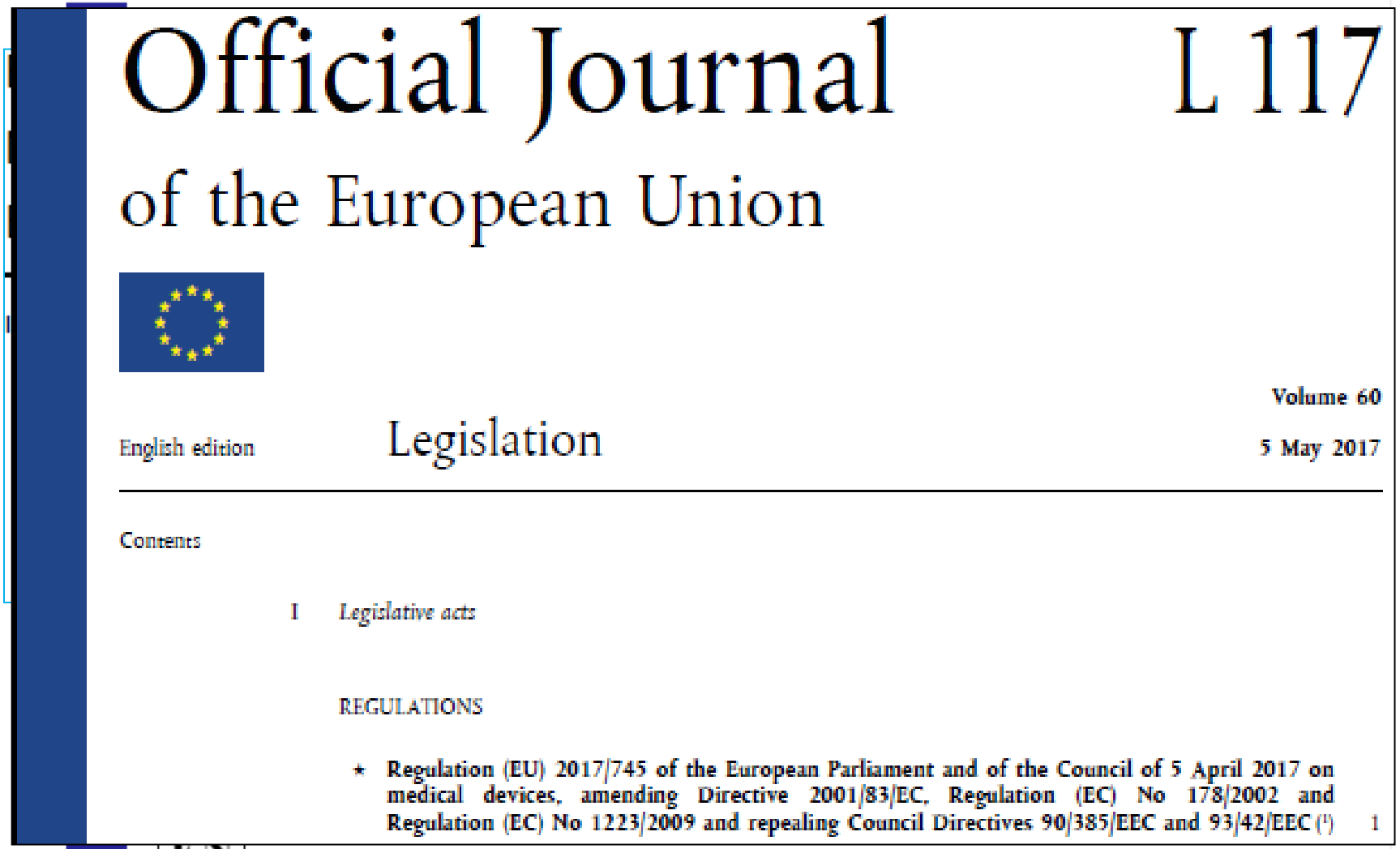
1) Introduction

History: biocompatibility requirements for medical devices

- **1986**: *Tripartite Biocompatibility Guidance, Preclinical Safety Evaluation of Medical Devices* was developed
- **1990**: adopted by United States, Canada and United Kingdom

- **1992**: ISO/TC 194 published ***ISO 10993-1*** *Biological evaluation of medical devices – Evaluation & testing*
  - **1995**: US FDA modified Tripartite Guidance document, to achieve closer harmonization with ISO 10993 referred to as *General Program Memorandum G95-1* (Blue Book Memorandum). FDA = ISO + additional Requirements
- **2003**: ISO 10993-1 revised
- **2009**: ISO 10993-1 revised and title amended to add **"within a risk management process"**
  - **2016**: US FDA replaced G95-1 guidance with "Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"
- **2018**: ISO 10993-1 revised

1) Introduction



Official Journal L 117

of the European Union

English edition

Legislation

Volume 60

5 May 2017

Contents

I *Legislative acts*

REGULATIONS

★ **Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC (1)** 1

EN

limited period.

The titles of all other Acts are printed in bold type and preceded by an asterisk.

Top

2) Change in approach MDD → MDR

MDR – much more detailed & prescriptive

	AIMDD	MDD	MDR
Published	20/06/1990	14/06/1993	05/04/2017
In force	20/06/1995	14/06/1998	26/05/2020
Pages	35	60	175
Recitals	9	22	101
Articles	17	23	123
Annexes	IX	XII	XVI
Annex I (ERs / GSPRs)	16	13	23
Biocompatibility related	9	7.1, 7.2, 7.5	10.1, 10.2, 10.4, 10.6
Words (Biocompatibility)	~75	~375	~850

3) MDR change overview

MDD – Annex I:

7. Chemical, Physical and Biological Properties

7.1 material choice & compatibility → **10.1** material/substance choice & compatibility

7.2 contaminants & residues → **10.2** contaminants & residues

7.5 substances leaking / CMR / phthalates / risk assessment / labelling → **10.4.1 to 10.4.5** substances released / CMR & endocrine disrupting / risk & justification / guidance on CMR, phthalates & endocrine disruptors / labelling

AIMDD – Annex I:

9. Material choice, toxicity, compatibility

MDR – Annex I:

10. Chemical, Physical and Biological Properties

10.1 material/substance choice & compatibility

10.2 contaminants & residues

10.4.1 to 10.4.5 substances released / CMR & endocrine disrupting / risk & justification / guidance on CMR, phthalates & endocrine disruptors / labelling

10.6 particle size & properties / nanomaterials *New!!*

3) MDR change overview

MDR Annex I: GSPR #10 Chem., Phys. & Biol. properties

10.1. Devices shall be designed & manufactured in such a way as to **ensure** that the characteristics & performance requirements referred to in Chapter I are fulfilled. Particular attention shall be paid to:

was "guarantee"

- **(a)** the choice of materials **and substances** used, particularly as regards toxicity and, where relevant, flammability;
- **(b)** the compatibility between the materials **and substances** used and biological tissues, cells and body fluids, taking account of the intended purpose of the device **and, where relevant, absorption, distribution, metabolism and excretion**;
- ***(c)*** *the compatibility between the different parts of a device which consists of more than one implantable part;*
- **(d) the impact of processes on material properties;**

3) MDR change overview

MDR Annex I: GSPR #10 Chem., Phys. & Biol. properties

10.1. ……. Particular attention shall be paid to:

- ***(e)*** *where appropriate, the results of biophysical or modelling research the validity of which has been demonstrated beforehand;*
- ***(f)*** *the mechanical properties of the materials used, reflecting, where appropriate, matters such as strength, ductility, fracture resistance, wear resistance and fatigue resistance;*
- **(g) surface properties**; and
- **(h) the confirmation that the device meets any defined chemical and/or physical specifications**

3) MDR change overview

MDR Annex I: GSPR #10 Chem., Phys. & Biol. properties

- **10.4.1.** Devices … designed and manufactured … to ***reduce as far as possible*** the risks posed by substances **or particles, including wear debris, degradation products and processing residues, that may be released** … **was "minimise"**
- Devices, or …parts thereof or …materials used therein that:
  - **are invasive and come into direct contact with the human body**,
  - (re)administer medicines, body liquids or other substances, including gases, to/from the body, or
  - transport or store such medicines, body fluids or substances, including gases, to be (re)administered to the body

  shall only contain *where* ***justified*** *as per 10.4.2.* **>0.1% (w/w)** of **substances which are:**
  - carcinogenic, mutagenic or toxic to reproduction (CMR), or
  - with **endocrine-disrupting properties**

  Was just phthalates with CMR properties in MDD

3) MDR change overview

MDR Annex I: GSPR #10 Chem., Phys. & Biol. properties

– **10.6**. Devices shall be designed and manufactured in such a way as to reduce as far as possible the **risks linked to the size and the properties of particles** which **are or can be released into the patient's or user's body**, unless they come into contact with intact skin only. Special attention shall be given to **nanomaterials**.

This is part of the Physical Characterisation

3) MDR change overview

MDR Annex I: GSPR#23 – Information for IFU

23.4 The instructions for use shall contain all of the following particulars: …

(u) in the case of implantable devices, the **overall qualitative and quantitative information** on the materials and substances to which patients can be exposed

3) MDR change overview

MDR Annex II: – Technical Documentation

6.1 Pre-clinical and clinical data

(b) detailed information regarding test design, complete test or study protocols, methods of data analysis, in addition to data summaries and test conclusions regarding in particular:

— the biocompatibility of the device including the **identification of all materials** in direct or indirect contact with the patient or user;

— **physical**, **chemical** and microbiological **characterisation**

3) MDR change overview

MDR Annex II: – Technical Documentation

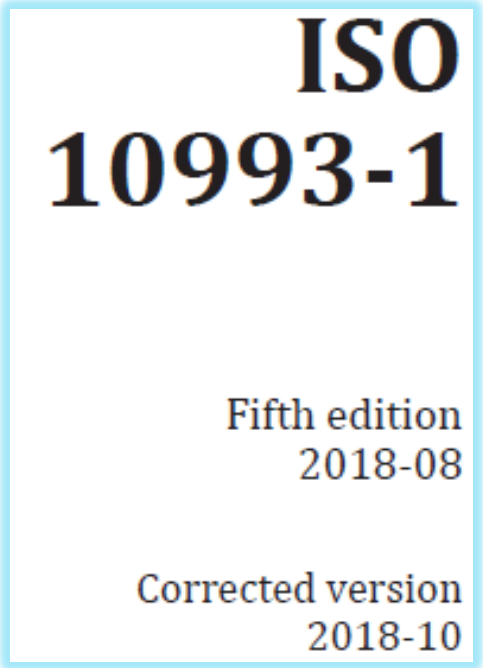
6.2 Additional information required in specific cases

(e) In the case of devices placed on the market in a sterile or defined microbiological condition, …The validation report shall address …., **pyrogen testing** …., **sterilant residues**.

4) Key ISO 10993-1:2018 changes

ISO 10993-1:2018 :

- Not yet listed as European standard on the CEN website or harmonized per Official Journal (last issue for MDD/AIMDD November 2017)
- Harmonization under MDR unclear….
  *…..deadline = 27/05/**2024*** …but is considered "***state-of-the-art***"
- **Closely aligned with the MDR**



4) Key ISO 10993-1:2018 changes

Table A.1 — Endpoints to be addressed in a biological risk assessment

Medical device categorization by			Endpoints of biological evaluation														
Nature of body contact		Contact duration															
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – Long term (>30 d)	Physical and/or chemical information	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Material mediated pyrogenicity[a]	Acute systemic toxicity[b]	Subacute toxicity[b]	Subchronic toxicity[b]	Chronic toxicity[b]	Implantation effects[b,c]	Hemocompatibility	Genotoxicity[d]	Carcinogenicity[d]	Reproductive/developmental toxicity[d,e]	Degradation[f]
Surface medical device	Intact skin	A	X[g]	E[h]	E	E											
		B	X	E	E	E											
		C	X	E	E	E											
	Mucosal membrane	A	X	E	E	E											
		B	X	E	E	E		E	E			E					
		C	X	E	E	E		E	E	E	E	E		E			
	Breached or compromised surface	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E					
		C	X	E	E	E	E	E	E	E	E	E		E	E		
Externally communicating medical device	Blood path, indirect	A	X	E	E	E	E	E					E				
		B	X	E	E	E	E	E	E				E				
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		
	Tissue/bone/dentin[i]	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E		E			
		C	X	E	E	E	E	E	E	E	E	E		E	E		
	Circulating blood	A	X	E	E	E	E	E					E	E[i]			
		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		
Implant medical device	Tissue/bone[i]	A	X	E	E	E	E	E									
		B	X	E	E	E	E	E	E			E		E			
		C	X	E	E	E	E	E	E	E	E	E		E	E		
	Blood	A	X	E	E	E	E	E				E	E	E			
		B	X	E	E	E	E	E	E			E	E	E			
		C	X	E	E	E	E	E	E	E	E	E	E	E	E		

4) Key ISO 10993-1:2018 changes

ISO 10993-1:2018 new requirements include:

4.1 evaluate advantages / disadvantages and relevance of:

a) device **configuration**, **qualitative list of materials** of construction, where necessary the proportion & amount (mass)

b) **physical/chemical characteristics** of materials of construction and their composition

4.3 c) **Packaging materials** in device contact

4.3 h) & **6.1** **particle** size (incl. nano) and wear particles

4.7 Biological safety over **whole life-cycle**

4.8 Biological safety over **maximum number of validated processing cycles** (reusable/reprocessable devices)

A.1 Additional **Endpoints** to consider

4) Key ISO 10993-1:2018 changes

ISO 10993-1:2018 – 4.11 Appropriate data for safe history of use

Regulatory approval ≠ no biological effects

Complaint analysis alone is usually **not sufficient**

Consideration of all available PMS data (PMCF studies, literature search, complaint / incident / AE analysis, registries, etc.)

Data need to be **appropriate** for the respective endpoint (not possible for some endpoints, e.g. genotoxicity)

Data relevance for current status of the device & patient group

4) Key ISO 10993-1:2018 changes

Chemical / physical characterisation standards

- **ISO 10993-17:2002** Biological evaluation of medical devices - Part 17: Establishment of allowable limits for leachable substances
- **ISO 10993-18:2020** Biological evaluation of medical devices - Part 18: Chemical characterization of materials
- **ISO/TS 10993-19:2006** Biological evaluation of medical devices - Part 19: Physico-chemical, morphological and topographical characterization of materials

5) Summary and Conclusion

Summary (NB expectation

– Meet “State-of-the-art”

– Meet GSPRs – *evidence*

– Meet 2018 edition of ISO 10993-1

- Chemical and physical information needed (MDD and MDR)
- Know which additional endpoints are applicable
- Justify any omission of further testing *(but be cautious about using a “safe history of clinical use”)*
- Assess over the full lifecycle (incl. *all* reprocessing)
- Proper biological safety evaluation – evidence!!

– MDD: 2018 version still SOTA but pragmatic transition

- Evaluate changes against 2018 version

Henry Sibun Associates

TÜV SÜD Product Service NB# 0123

Presafe A DNV GL COMPANY NB# 2460

DEKRA NB# 0124 NB# 0344

TÜVRheinland LGA NB# 0197

IMQ NB# 0051

NSAI NB# 0050

bsi. NB# 2797 NB# 0086

MEDCERT Certification. Medical Only. NB# 0482

DARE!! NB# 1912

5) Summary and Conclusion

Conclusion

- MDR and ISO 10993-1:2018 closely aligned
- Understand how changes affect your products
- Gap analysis (documented) and address additional requirements for MDR and ISO 10993-1:2018
- *Biological evaluation report without any chemical (and if necessary physical) information is not acceptable anymore under either the MDD/AIMDD or the MDR*
- For MDD – changes need to meet ISO 10993-1:2018
- NBs very busy – expect delays & present BSE that is complete and clear!

Thank You

Henry Sibun
ASSOCIATES

Tel: +44 1404 813099 Mob: +44 7836 329863
henry@henrysibun.com www.henrysibun.com