BIOCOMPATIBILITY UNDER A RISK MANAGEMENT APPROACH- CURRENT EXPECTATIONS AND BEST PRACTICE”

DR. VINCENT LEGAY
MANAGER EUROPE, CONSULTING SERVICES
NAMSA

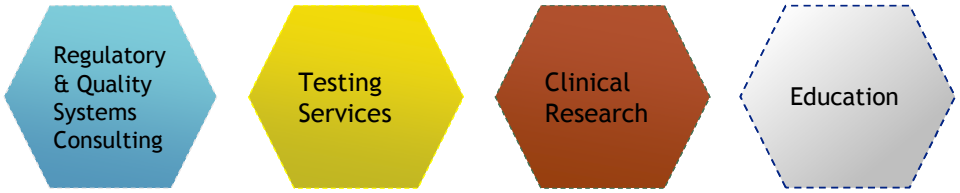
DÉCLARATION DE LIENS D'INTÉRÊT

Opinion and proposal reflected in this presentation only engage the author.

NAMSA

- Global Regulatory Strategy & Assessment
- Pre-Submission meetings
- Functional & Efficacy studies
- Design Controls
- Preclinical Research & Model Development
- Test Method Development & Validation
- Quality Systems/ Quality Management
- Biocompatibility
- Materials Characterization and Risk Assessment
- Packaging Validations
- Study Design & Management
- Biostatistics
- Data Management
- Report writing
- DSMB/CEC
- Physician Training
- IDE Submissions
- Global Marketing Applications
- FDA BIMO Inspections
- FDA Panel Meetings
- Post-Market Clinical Trials & Registries
- Microbiology Testing
- Sterilization Assurance
- FDA Reporting Requirements
- Training Seminars

NAMSA Education



ISO 10993-1 (2009/Cor1: 2010)

➥ **Evaluation and testing within a risk management process**

Framework to **plan** a **biological evaluation:**

- minimizes the number and exposure of **test animals**

- gives preference to **chemical characterization**

New concept:

- from **which biocompatibility tests** should be conducted

- to a **global approach** that considers **all existing information** prior to determining if chemistry and/or biocompatibility testing is needed

ISO 10993-1 (2009/Cor1: 2010)

Clause 4.1: “ *The biological evaluation of any material or medical device intended for use in human shall form part of a* ***structured biological evaluation programme within a risk management process*** *in accordance with ISO 14971***”**

→ **Biological Risk Assessment**

ISO 14971 (2007) / EN ISO 14971 (2012)

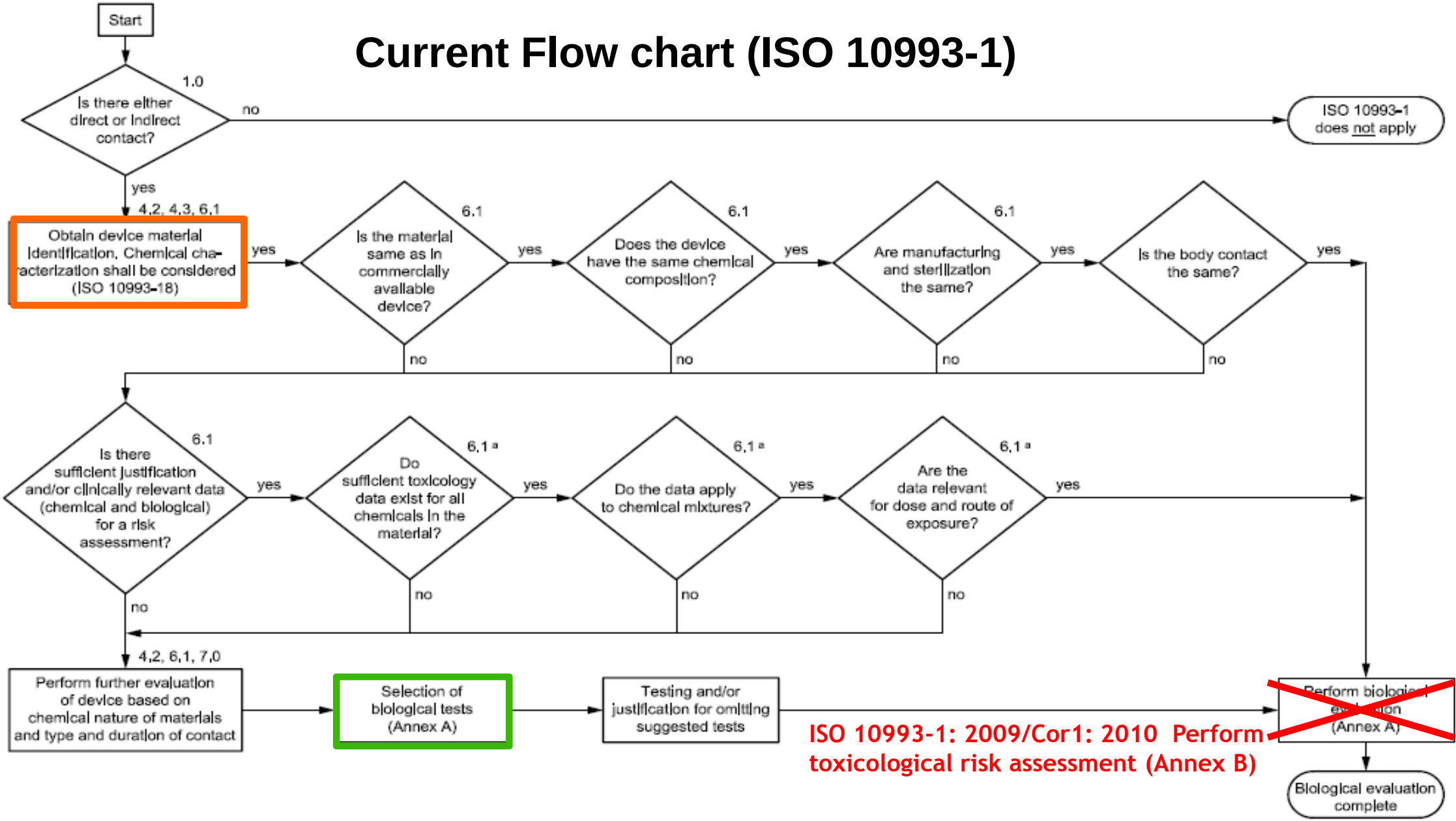
➥ **Application of risk management to medical devices**

Biological evaluation of a medical device is a component of risk management = Conduct of a biological evaluation should aim to meet both the requirements of ISO 10993-1 and ISO 14971

- Risk Analysis
- Risk Evaluation
- Risk Control
- Overall Risk Evaluation
- Consideration of Production and Post-Production Information

➡ **Biological Risk Assessment**

Current Flow chart (ISO 10993-1)



ISO 10993-1: 2009/Cor1: 2010 Perform toxicological risk assessment (Annex B)

Medical device categorization by — Endpoints of biological evaluation

Nature of Body Contact		Contact Duration	Physical and/or chemical information	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Material mediated pyrogenicity [a]	Acute systemic toxicity	Subacute toxicity	Subchronic toxicity	Chronic toxicity	Implantation [b]	Hemocompatibility	Genotoxicity	Carcinogenicity	Reproductive/developmental toxicity [c]	Biodegradation [d]
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – Long term (> 30 d)															
Surface device	Intact skin	A	X [e]	E [f]	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			E					
		C	X	E	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		
External communicating 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 [g]	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 [h]			
		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 device	Tissue/ bone	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		

[a] Refer to ISO 10993-11 Annex F.

[b] Relevant implantation routes should be considered. For instance devices in contact with intact mucosal membranes should ideally be studied/ considered in contact with intact mucosal membranes.

[c] Reproductive and developmental toxicity should be addressed for novel materials, materials with a known reproductive or developmental toxicity, devices with relevant target populations (e.g., pregnant women), and/or devices where there is the potential for local presence of device materials in the reproductive organs.

[d] Biodegradation information should be provided for any devices, device components or materials remaining within the patient, that have the potential for degradation.

[e] X means prerequisite information needed for a risk assessment.

[f] E means endpoints to be evaluated in the risk assessment (either through the use of existing data, additional endpoint-specific testing, or a rationale for why the endpoint does not require additional assessment).

[g] Tissue includes tissue fluids and subcutaneous spaces. For gas pathway devices or components with only indirect tissue contact, see device specific standards for biocompatibility information relevant to these devices. Information obtained from Implantation assessments can be appropriate to address acute systemic toxicity, subacute toxicity, subchronic toxicity and chronic toxicity.

ISO CD 10993-1
June 2016

DEVICE CATEGORIES		CHEMICAL/MATERIAL CHARACTERIZATION TEST PROCEDURES																
					Organic Additive Identification						Physical Tests			Mol. Weight				
BODY CONTACT		Exhaustive Extraction	Physicochemical	FTIR	HPLC-MS	HPLC-IC	GC Headspace	GC-FID	GC-MS	ICP	Physical/Mechanical	Specific Gravity	Durometer Hardness	GPC	Viscosity	SEM/XRD	DSC
SURFACE DEVICES	SKIN		E	E/M													
	MUCOSAL MEMBRANE		E	E/M													
	BREACHED OR COMPROMISED SURFACES		E	E/M													
EXTERNALLY COMMUNICATING DEVICES	BLOOD PATH, INDIRECT		E	E/M	E	E	E	E	E	E	M						P
	TISSUE/ BONE/DENTIN COMMUNICATING		E	E/M	E	E	E	E	E	E	M						P
	CIRCULATING BLOOD	E	E	E/M	E	E	E	E	E	E	M	M	P	P	P	M	P
IMPLANT DEVICES	TISSUE/BONE	E	E	E/M	E	E	E	E	E	E	M	M	P	P	P	M	P
	BLOOD	E	E	E/M	E	E	E	E	E	E	M	M	P	P	P	M	P

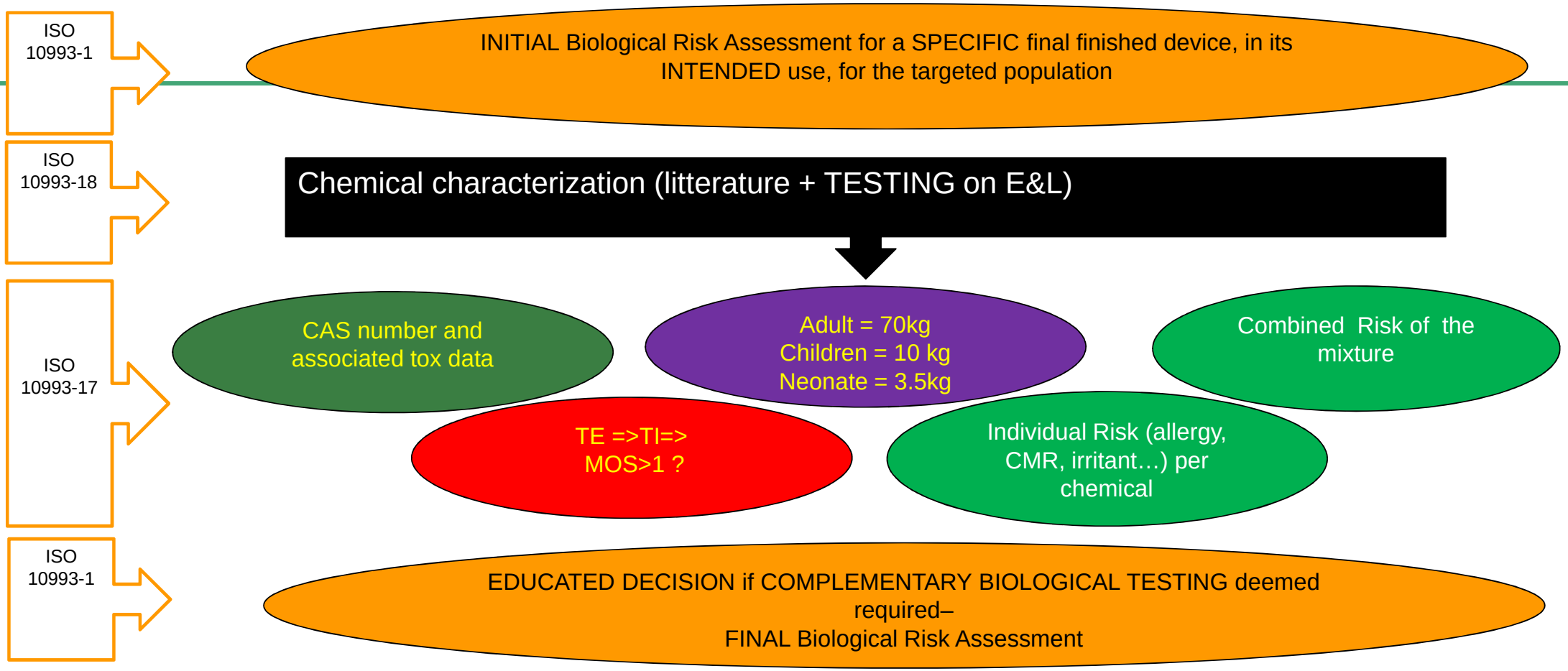
E = extractable: an extract of the device is prepared and characterized resulting in a fingerprint which can be interpreted as being bioavailable.

M = material: (ceramics, metals and polymeric materials). The device component is dissolved in an appropriate solvent and used for characterization of all constituents of that component. Typically performed for complete compositional analysis, including all additives.

P = Polymeric material: the individual unaltered device component is used for characterization. Test procedures indicated with P are appropriate for polymeric materials only.

EDUCATED DECISION ABOUT IF THERE IS ANY CHEMICAL DETECTED (QUALITATIVE) AT A DOSE (QUANTITATIVE) CAPABLE OF CAUSING A BIOLOGICAL RISK FOR THE TARGETED POPULATION?

Using ISO 10993-17 Toxicological assessment, EDUCATED DECISION about if there is any chemical detected (QUALITATIVE) at a DOSE (QUANTITATIVE) capable of causing a BIOLOGICAL risk for the targeted POPULATION?



Tips for avoiding pitfalls in the safety evaluation of a medical device

- **Writing a Biological Risk Assessment**
  - **Nature, degree, duration and frequency of contact**
  - **Raw materials and manufacturing processes**
  - **Clinical history of use adressing some risks ?**
  - **Physico-chemical characterization**
  - **Innovative characteristics**
  - **Market place (Europe, US, Japan, China, …)**
    - **Case by case approach**

Thank you

NAMSA
Global Headquarters
6750 Wales Road
Northwood, OH 43619 USA

For more information, please contact:

Vincent Legay
vlegay@namsa.com
0033 6 24 24 31 24