Risk-appropriate Chemical Characterization to Support Biological Evaluations

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Biological Evaluations

A step-wise process to determine patient safety

- Biological evaluation process for patient safety is based on the evaluation of risk for which chemical characterization is a key element.
- Degree of chemical characterization is dependent on risk categories of the device. *This is largely defined by the device contact category.*

Risk Based Approach
Biological Evaluation Overview

RISK ANALYSIS

- Information gathering (physical form e.g., geometry, particle size, porosity) & chemical constituents of the material and manufacturing processes
- Identification of biological hazards (based on ISO Part 1)
- Determine Intended Use Category (clinical use, nature of contact and duration) of the Device under Evaluation

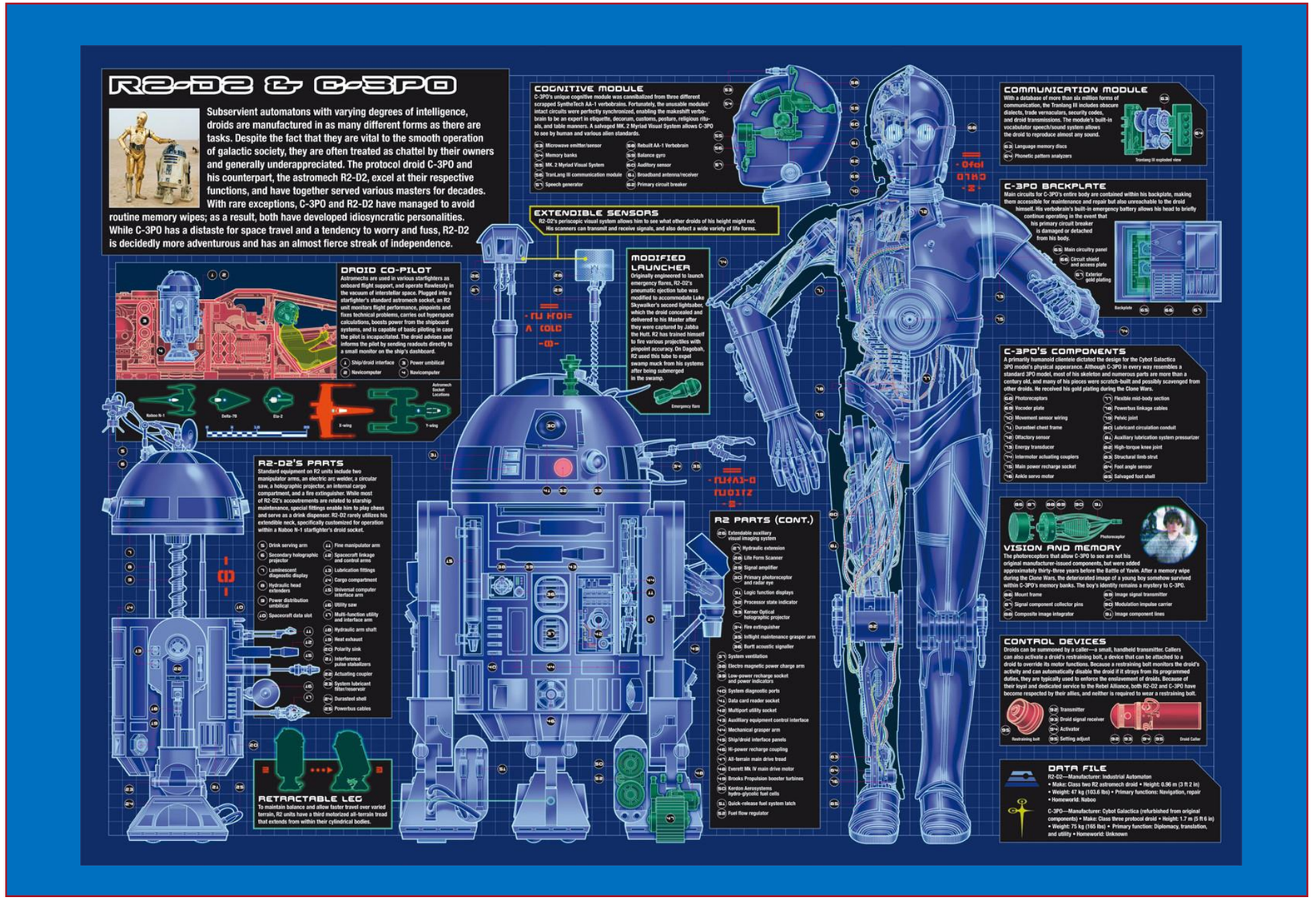
RISK EVALUATION

- Based on intended use and device characteristics
- Leverage previous safety data when justified
- Conduct overall biological risk assessment, determine equivalency based on similar **device, chemical, physical, material/manufacturing processes, clincal use, & biological endpoints.**
- Step wise approach considered (Physical and chemical characterization, Toxicological Risk Assessment, Chemical testing, In vitro & In vivo data)
- Include risk control measures, documentation of any residual risks and determination of need for disclosure of residual risks (e.g., through means such as product labelling)

RISK CONTROL

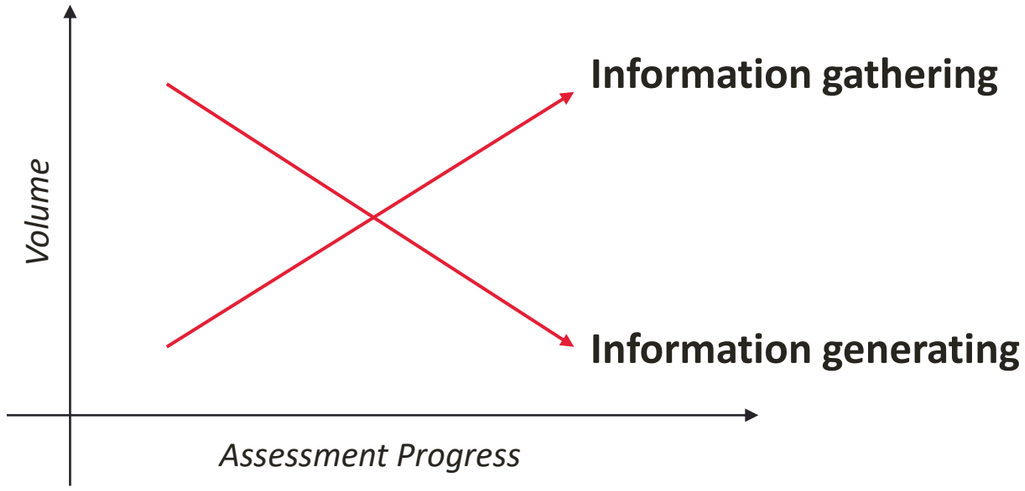
- Mitigating risks through evaluation by testing or by presenting justification for omission of testing
- Conduct any additional testing if necessary
- Document all information on the device, description, processing toxicity and biological testing data and risk conclusion in a Biological Evaluation Report (BER)

One Size Fits All **BLUEPRINTS** for Chemical Characterisation



Information gathering

Process of collecting existing chemical information, including available test results, that is relevant to chemical characterization.



Information generation

Process of producing chemical information via laboratory testing.

How much information is enough?

Two Components

- *Quality of Available information*
- *Device Risk Category*

INTERNATIONAL STANDARD

ISO 10993-1

Fifth edition
2018-08

Corrected version
2018-10

Biological evaluation of medical devices —

Part 1:
Evaluation and testing within a risk management process

Évaluation biologique des dispositifs médicaux —

Partie 1: Évaluation et essais au sein d'un processus de gestion du risque

Biological evaluation of medical devices —

Part 1:
Evaluation and testing within a risk management process

1 Scope

This document specifies:

— the general principles governing the biological evaluation of medical devices within a risk management process;

— the general categorization of medical devices based on the nature and duration of their contact with the body;

— the evaluation of existing relevant data from all sources;

— the identification of gaps in the available data set on the basis of a risk analysis;

— the identification of additional data sets necessary to analyse the biological safety of the medical device;

— the assessment of the biological safety of the medical device.

This document applies to evaluation of materials and medical devices that are expected to have direct or indirect contact with:

— the patient's body during intended use;

— the user's body, if the medical device is intended for protection (e.g., surgical gloves, masks and others).

This document is applicable to biological evaluation of all types of medical devices including active, non-active, implantable and non-implantable medical devices.

This document also gives guidelines for the assessment of biological hazards arising from:

— risks, such as changes to the medical device over time, as a part of the overall biological safety assessment;

— breakage of a medical device or medical device component which exposes body tissue to new or novel materials.

Other parts of ISO 10993 cover specific aspects of biological assessments and related tests. Device-specific or product standards address mechanical testing.

This document excludes hazards related to bacteria, moulds, yeasts, viruses, transmissible spongiform encephalopathy (TSE) agents and other pathogens.

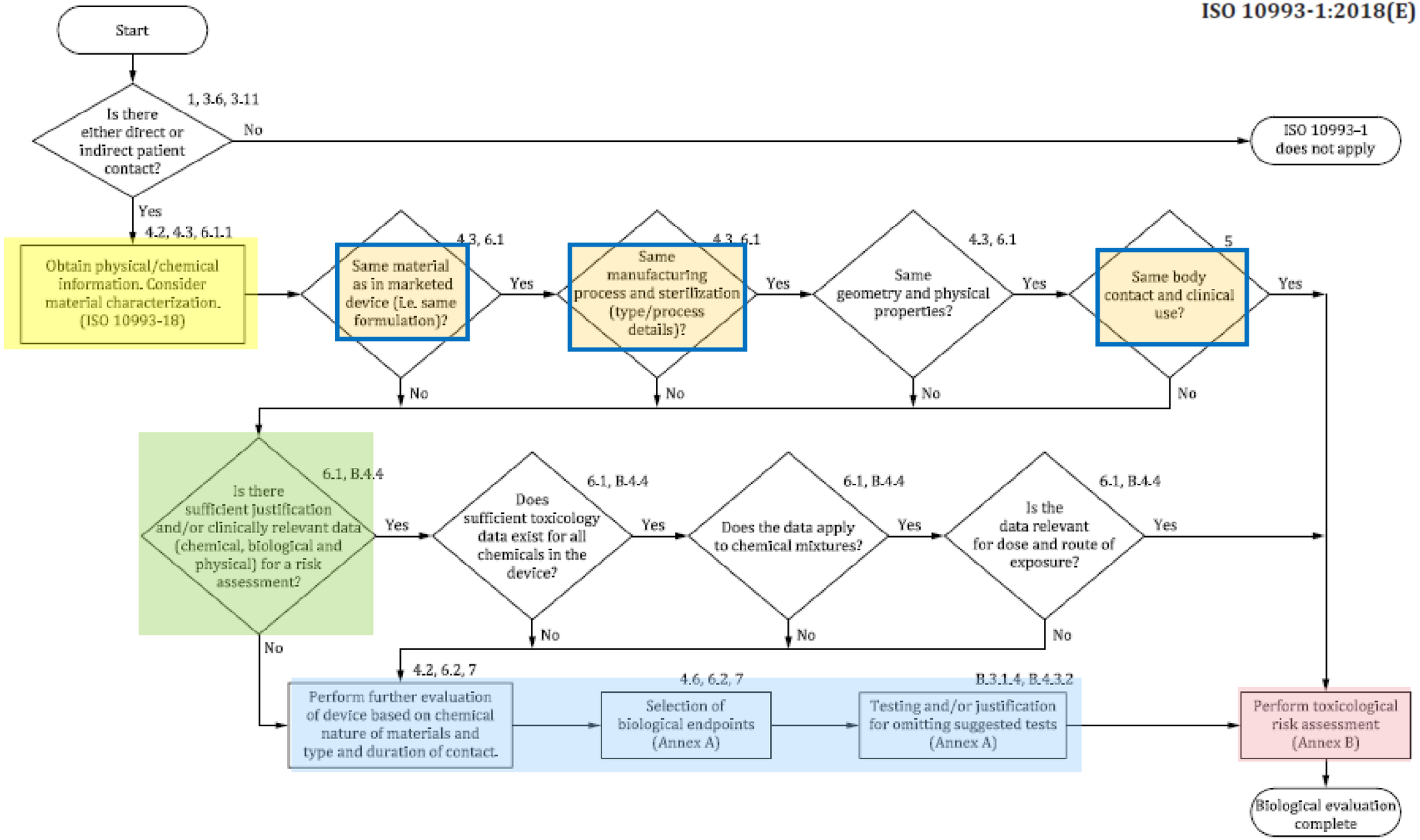


Figure 1 — Summary of the systematic approach to a biological evaluation of medical devices as part of a risk management process

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[j]			
		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		

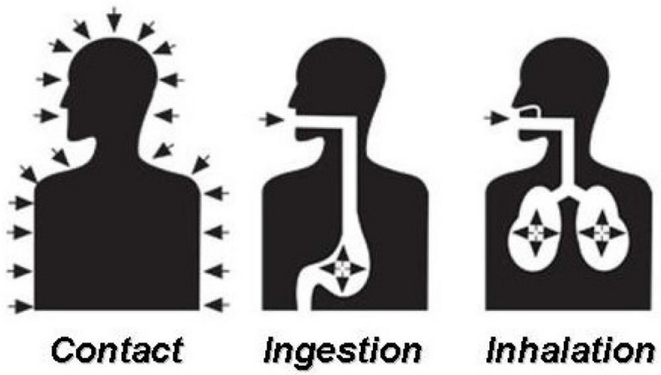
Medical device categorization by

Nature of body contact

Contact duration

Medical device categorization by		
Nature of body contact		Contact duration
Category	Contact	**A – limited** (≤24 h) **B – prolonged** (>24 h to 30 d) **C – Long term** (>30 d)
Surface medical device	Intact skin	A
		B
		C
	Mucosal membrane	A
		B
		C
	Breached or compromised surface	A
		B
		C

Varying routes through which exposure can occur.



Magnitude, duration, & freq.

Device Risk Categories

- *As per ISO 10993-1, risk is associated with categories of device contact and duration.*

Intact Skin

Breached, Compromised surface

Mucosal membrane

Tissue/Bone/Dentin

Blood path (indirect)

Breached, Compromised surface
Prolonged Duration

Mucosal membranes
Prolonged Duration

Blood path (indirect)
Prolonged Duration

Circulating blood
**Limited and Prolonged Duration*

Tissue/Bone/Dentin
Prolonged Duration

Breached/Compromised surface

Mucosal membranes

Tissue/Bone/Dentin

Blood path (indirect)

Circulating blood

VERY LOW RISK | **RISK LEVEL 1**

Intact Skin

Limited, Prolonged or Long-Term Duration

Examples

- Electrodes
- Fixation tapes
- Compression bandages

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																
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		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		

Risk Level

1

Chemical Characterization

Document available biological and chemical information.

Additional chemical testing likely will provide limited added value to biological test data for safety determination

LOW RISK | **RISK LEVEL 2**

Breached/Compromised Surface, Mucosal Membrane, Tissue/bone/dentin, Blood path (indirect)

Limited duration

Examples

Devices contacting breached, compromised surface
Dressings or healing devices and occlusive patches for ulcers, burns and granulation tissue.

Devices contacting mucosal membranes
Urinary catheters, intravaginal and intra-intestinal devices, endotracheal tubes, bronchoscopes, and orthodontic devices.

Devices that contact tissue, bone or dentin
Laparoscopes, arthroscopes, draining systems, dental filling materials and skin staples.

Devices that contact blood path, indirect
Solution administration sets, extension sets, transfer sets and blood administration sets.

Risk Level

2

Chemical Characterization

Document available biological and chemical information.

Additional chemical testing may have limited value. **Focus on "surface" chemistry**

MEDIUM RISK | **RISK LEVEL 3**

Breached/Compromised surface, Mucosal membranes, Blood path (indirect), Circulating blood*, Tissue/Bone/Dentin

Prolonged Duration

*(*includes Limited)*

Examples

Devices contacting breached, compromised surface
Dressings or healing devices and occlusive patches for ulcers, burns and granulation tissue.

Devices contacting mucosal membranes
Urinary catheters, intravaginal and intra-intestinal devices, endotracheal tubes, bronchoscopes and orthodontic devices.

Devices that contact blood path, indirect
Solution administration sets, extension sets, transfer sets and blood administration sets.

Devices that contact circulating blood
Intravascular catheters, temporary pacemaker electrodes, oxygenators, extracorporeal oxygenator tubing and accessories, dialysers, dialysis tubing and accessories, haemoadsorbents and immunoadsorbents.

Devices that contact tissue, bone or dentin
Laparoscopes, arthroscopes, draining systems, dental filling materials and skin staples.

Risk Level

3

Chemical Characterization

Document available biological and chemical information.

Extractable testing can be used to address Acute, Sub-Acute, Sub-Chronic Systemic Toxicity, & Genotoxicity

CardinalHealth™

HIGH RISK | **RISK LEVEL 4**

Breached/Compromised surface, Tissue/bone/dentin Blood path (indirect), Circulating blood*

Long-term Duration

(includes Prolonged)*

Examples

Devices that contact breached, compromised surface
Dressings or healing devices and occlusive patches for ulcers, burns and granulation tissue.

Devices that contact blood path, indirect
Solution administration sets, extension sets, transfer sets and blood administration sets.

Devices that contact circulating blood
Intravascular catheters, temporary pacemaker electrodes, oxygenators, extracorporeal oxygenator tubing and accessories, dialysers, dialysis tubing and accessories, haemoadsorbents and immunoadsorbents.

Devices that contact tissue, bone or dentin
Laparoscopes, arthroscopes, draining systems, dental filling materials and skin staples.

Risk Level

4

Chemical Characterization

Document available biological and chemical information.

Extractable testing can be used to address Acute, Sub-Acute, Sub-Chronic, and Chronic Systemic Toxicity, Genotoxicity, & Carcinogenicity

HIGH RISK | **RISK LEVEL 4**

Extractables/Leachables Testing

Risk Level

4

Extraction Method

- Simulated Use (specified duration, based on clinical use)
- Exaggerated
  - single use devices used for less than 24h, where repeat use of a new device each day would result in categorization as prolonged or long-term contact;
  - single use devices used for several days, where repeat use of new devices would result in categorization as prolonged or long-term contact;
  - reusable devices, where a patient may be exposed to repeated use of the same device, resulting in categorization as prolonged or long-term contact; when an exaggerated extraction is used for a reusable device, the extraction should properly account for the duration of each individual use.
- Exhaustive
  - If conditions above are not adequate

Consider duration of device exposure to Patient when determining extraction conditions

Analytical Methods – *Type of material will guide analytical method*

- Metals – elemental analytical methods
- Synthetic polymers – organic compound analytical methods

Device Risk Categories and Chemical Characterization

As per ISO 10993-1, risk is defined in categories of device contact and duration.

Document available biological and chemical information.

Additional chemical testing will provide limited added value to biological test data

Document available biological and chemical information.

Additional chemical testing has limited value. Focus on surface chemistry

Document available biological and chemical information.

Additional chemical testing to address Acute, Sub-Acute, Sub-Chronic Systemic Toxicity, Genotoxicity

Document available biological and chemical information.

Additional chemical testing to address Acute, Sub-Acute, Sub-Chronic, Chronic Systemic Toxicity, Genotoxicity, Carcinogenicity

Focus on adequately protective:

Biological Evaluation at varying risk levels – Assessing Endpoints through levels of Chemical Characterization

Very Low Risk	Low to Medium Risk	High Risk
• Cytotoxicity • Sensitization • Irritation	• Cytotoxicity • Sensitization • Irritation • Systemic Toxicity (acute, subacute, subchronic) • Genotoxicity	• Cytotoxicity • Sensitization • Irritation • Systemic Toxicity (acute, subacute/ subchronic & chronic) • Pyrogenicity • Implantation • Genotoxicity • Carcinogenicity • Reproductive toxicity

CHEMICAL CHARACTERISATION

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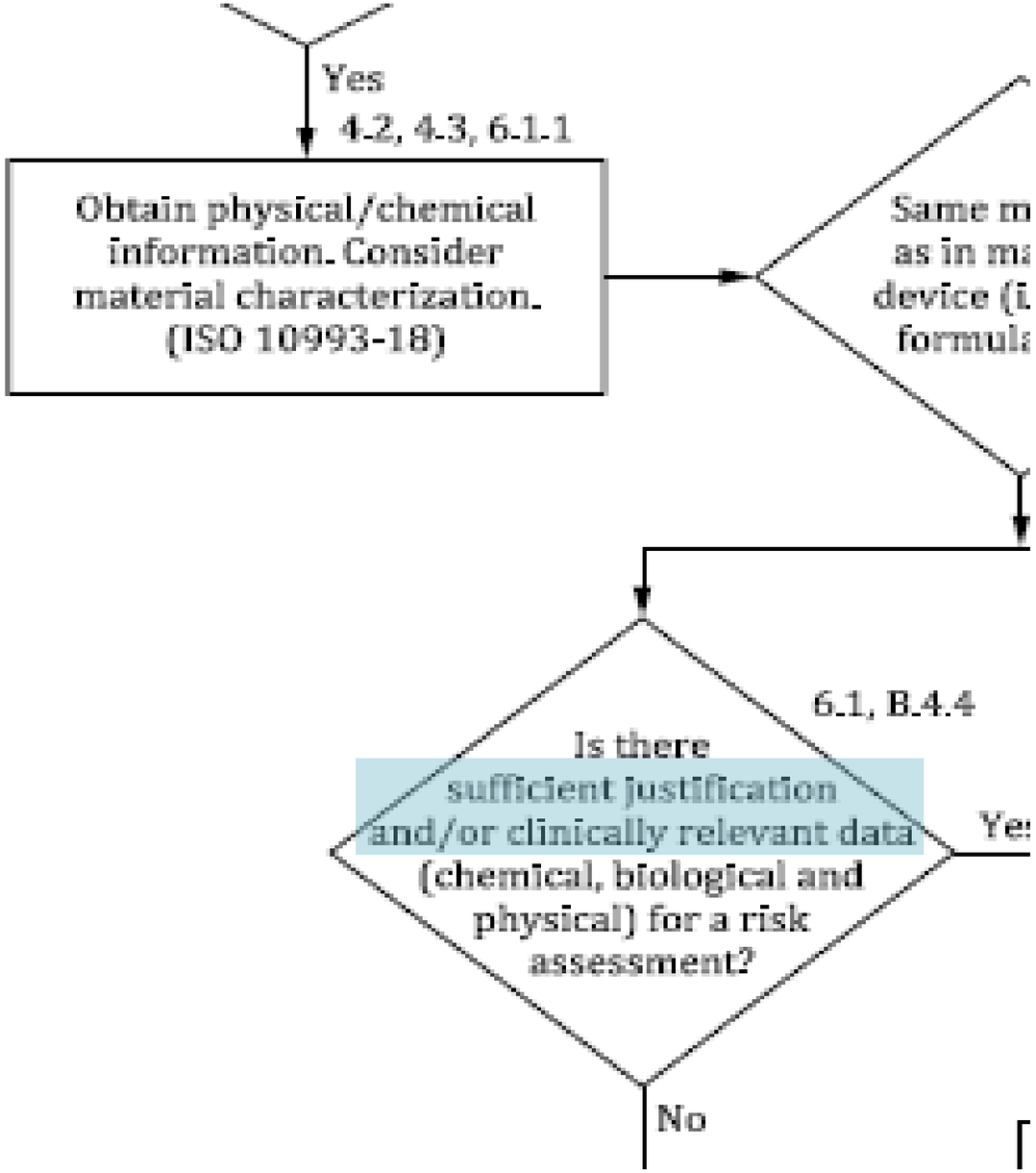
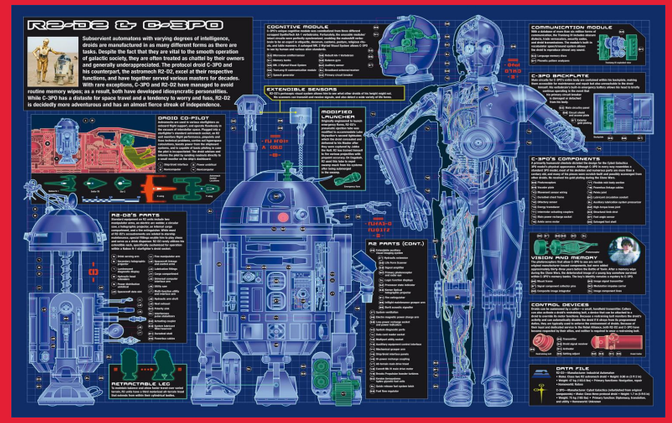


The BluePrints for Chemical Characterisation



How much info is enough?

Two Components

- *Quality of Available information*
- *Device Risk Category*

Several considerations regarding quality of chemical info

Risk Level	Chemical information that may be suitable for supporting Safety evaluation
Very Low risk	Bill of Materials, Known additives, Manufacturing processing aids, manufacturing processes and storage conditions (understanding potential resulting compounds), safety data sheets
Low risk	All Chem Information from Very Low Risk **AND "**Surface" Chemistry (e.g. residuals) analysis *MAY* be adequate *(consider material science and clinical use)*
Medium risk	Adequately protective quantitation of Chemical Constituents present in and on the device post manufacturing and exposed to the patient during clinical use **OR** Adequately Protective "Extractable" study
High risk	Quantitative details of Chemical Constituents present in and on the device post manufacturing **AND** "leachable" study **OR** Adequately protective "Extractable" study

Thank you

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