



Risk-appropriate Chemical Characterization to Support Biological Evaluations

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John Iannone

Global Head of Biocompatibility, Toxicology, Chemistry, Sterility, & Microbiology – QRA

- 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.*

Biological Evaluations

A step-wise process to determine patient safety

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, clinical 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

R2-D2 & C-3PO

Subservient automatons with varying degrees of intelligence, droids are manufactured in as many different forms as there are tasks. Despite the fact that they are vital to the smooth operation of galactic society, they are often treated as chattel by their owners and generally underappreciated. The protocol droid C-3PO and his counterpart, the astromech R2-D2, excel at their respective functions, and have together served various masters for decades. With rare exceptions, C-3PO and R2-D2 have managed to avoid routine memory wipes; as a result, both have developed idiosyncratic personalities. While C-3PO has a distaste for space travel and a tendency to worry and fuss, R2-D2 is decidedly more adventurous and has an almost fierce streak of independence.

COGNITIVE MODULE

C-3PO's unique cognitive module was cannibalized from three different scrapped SynthTech AA-1 verobrain. Fortunately, the unusable modules' intact circuits were perfectly synchronized, enabling the malleable verobrain to be an expert in etiquette, decorum, customs, posture, religious rituals, and table manners. A salvaged MK 2 Mystical Visual System allows C-3PO to see by human and various alien standards.

- ① Memory center/sensor
- ② Memory banks
- ③ MK 2 Mystical Visual System
- ④ StarLang III communication module
- ⑤ Speech generator
- ⑥ Result A-1 Verobrain
- ⑦ Balance arm
- ⑧ Auditory sensor
- ⑨ Broadband antenna/receiver
- ⑩ Primary circuit breaker

EXTENSIBLE SENSORS

R2-D2's portoscopic visual system allows him to see what other droids of his height might not. His scanners can transmit and receive signals, and also detect a wide variety of life forms.

COMMUNICATION MODULE

With a database of more than six million forms of communication, the Trailing III includes obscure dialects, trade vernaculars, security codes, and droid transmissions. The module's built-in vocabulator speech/sound system allows the droid to reproduce almost any sound.

- ① Language memory discs
- ② Phonetic pattern analyzers

DROID CO-PILOT

Astromechs are used in various starfighters as onboard flight support, and operate flawlessly in the vacuum of interstellar space. Pipped into a starfighter's standard astromech socket, an R2 unit monitors flight performance, pinpoints and fixes technical problems, carries out hyperpace calculations, boosts power from the shipboard systems, and is capable of basic piloting in case the pilot is incapacitated. The droid advises and informs the pilot by sending readouts directly to a small monitor on the ship's dashboard.

- ① Ship/droid interface
- ② Power umbilical
- ③ Navicomputer
- ④ Astromech Socket Location

MODIFIED LAUNCHER

Originally engineered to launch emergency flares, R2-D2's pneumatic ejection tube was modified to accommodate Luke Skywalker's second lightsaber, which the droid concealed and delivered to his Master after they were captured by Jabba the Hutt. R2 has trained himself to fire various projectiles with pinpoint accuracy. On Yavin 4, R2 used this tube to repel swamp muck from his systems after being submerged in the swamp.

C-3PO BACKPLATE

Main circuits for C-3PO's entire body are contained within his backplate, making them accessible for maintenance and repair but also unreachable to the droid himself. His withdrawal's built-in emergency battery allows his head to briefly continue operating in the event that his primary circuit breaker is damaged or detached from his body.

- ① Main circuitry panel
- ② Circuit shield and access plate
- ③ Colored wiring

R2-D2'S PARTS

Standard equipment on R2 units include two manipulator arms, an electric arc welder, a circular saw, a holographic projector, an internal cargo compartment, and a fire extinguisher. While most of R2-D2's accommodations are related to starship maintenance, special fittings enable him to play chess and serve as a drink dispenser. R2-D2 rarely utilizes his extendible neck, specifically customized for operation within a Habbok 1-1 starfighter's droid socket.

- ① Drink serving arm
- ② Secondary holographic projector
- ③ Lubrication fittings
- ④ Luminescent display
- ⑤ Hydraulic head stabilizers
- ⑥ Universal computer interface arm
- ⑦ Power distribution umbilical
- ⑧ Spacecraft data slot
- ⑨ Hydraulic arm shaft
- ⑩ Heat exhaust
- ⑪ Priority slot
- ⑫ Inertness pulse stabilizers
- ⑬ Actuating coupler
- ⑭ System lubricant filter/reverser
- ⑮ Duralaste shell
- ⑯ Powerbus cables
- ⑰ Fine manipulator arm
- ⑱ Spacecraft linkage and control arm
- ⑲ Cargo compartment
- ⑲ Hydraulic head stabilizers
- ⑲ Universal computer interface arm
- ⑲ Utility saw
- ⑲ Multi-function utility and interface arm
- ⑲ Heat exhaust
- ⑲ Priority slot
- ⑲ Inertness pulse stabilizers
- ⑲ Actuating coupler
- ⑲ System lubricant filter/reverser
- ⑲ Duralaste shell
- ⑲ Powerbus cables

R2 PARTS (CONT.)

- ① Extensible auxiliary visual imaging system
- ② Life Form Scanner
- ③ Signal amplifier
- ④ Primary photoreceptor and radar eye
- ⑤ Logic function displays
- ⑥ Processor state indicator
- ⑦ Kerner Optical holographic projector
- ⑧ Fire extinguisher
- ⑨ Built acoustic signalizer
- ⑩ System ventilation
- ⑪ Electro magnetic power charge arm
- ⑫ Low-power recharge socket and power indicators
- ⑬ System diagnostic parts
- ⑭ Data card reader socket
- ⑮ Multiport utility socket
- ⑯ Auxiliary equipment control interface
- ⑰ Mechanical grasper arm
- ⑱ Ship/droid interface panels
- ⑲ All-terrain main drive bread
- ⑲ Everet MK IV main drive motor
- ⑲ Brooki Propulsion booster turbines
- ⑲ Border Anemometers
- ⑲ Hydro-glycolic fuel cells
- ⑲ Quick-release fuel system latch
- ⑲ Fuel flow regulator

C-3PO'S COMPONENTS

A primary humuloid chassis, designed for the Cystol Galactic 3PO model's physical appearance. Although C-3PO in every way resembles a standard 3PO model, most of his skeleton and numerous parts are more than a century old, and many of his pieces were scratch-built and possibly scavenged from other droids. He received his gold plating during the Clone Wars.

- ① Photoreceptors
- ② Vocoder plate
- ③ Duralaste chest frame
- ④ Olfactory sensor
- ⑤ Energy transducer
- ⑥ Interceptor actuating couplers
- ⑦ Main power recharge socket
- ⑧ Ankle servo motor
- ⑨ Flexible mid-body section
- ⑩ Powerbus linkage cables
- ⑪ Pelvic joint
- ⑫ Lubricant circulation conduit
- ⑬ Auxiliary lubrication system pressurizer
- ⑭ High-torque knee joint
- ⑮ Structural link strut
- ⑯ Foot angle sensor
- ⑰ Salvaged foot shell

RETRACTABLE LEG

To maintain balance and allow faster travel over varied terrain, R2 units have a third motorized all-terrain tread that extends from within their cylindrical bodies.

VISION AND MEMORY

The photoreceptors that allow C-3PO to see are not his original manufacturer-based components, but were added approximately thirty-three years before the Battle of Yavin. After a memory wipe during the Clone Wars, the deteriorated image of a young boy somehow survived within C-3PO's memory banks. The boy's identity remains a mystery to C-3PO.

- ① Mount frame
- ② Signal component collector pins
- ③ Composite image integrator
- ④ Image component lens

CONTROL DEVICES

Droids can be immobilized by a collar—small, handheld transmitter. Collars can also activate a droid's restraining bolt, a device that can be attached to a droid to override its motor functions. Because a restraining bolt monitors the droid's activity and can automatically disable the droid if it strays from its programmed duties, they are typically used to enforce the enslavement of droids. Because of their loyal and dedicated service to the Rebel Alliance, both R2-D2 and C-3PO have become respected by their allies, and neither is required to wear a restraining bolt.

- ① Restraining bolt
- ② Transmitter
- ③ Droid signal receiver
- ④ Activator
- ⑤ Setting adjust
- ⑥ Droid Collar

DATA FILE

R2-D2—Manufacturer: Industrial Automaton
 • Make: Class two R2 astromech droid • Height: 0.96 m (3 ft 2 in)
 • Weight: 47 kg (103.6 lbs) • Primary functions: Navigation, repair
 • Homeworld: Tatooine

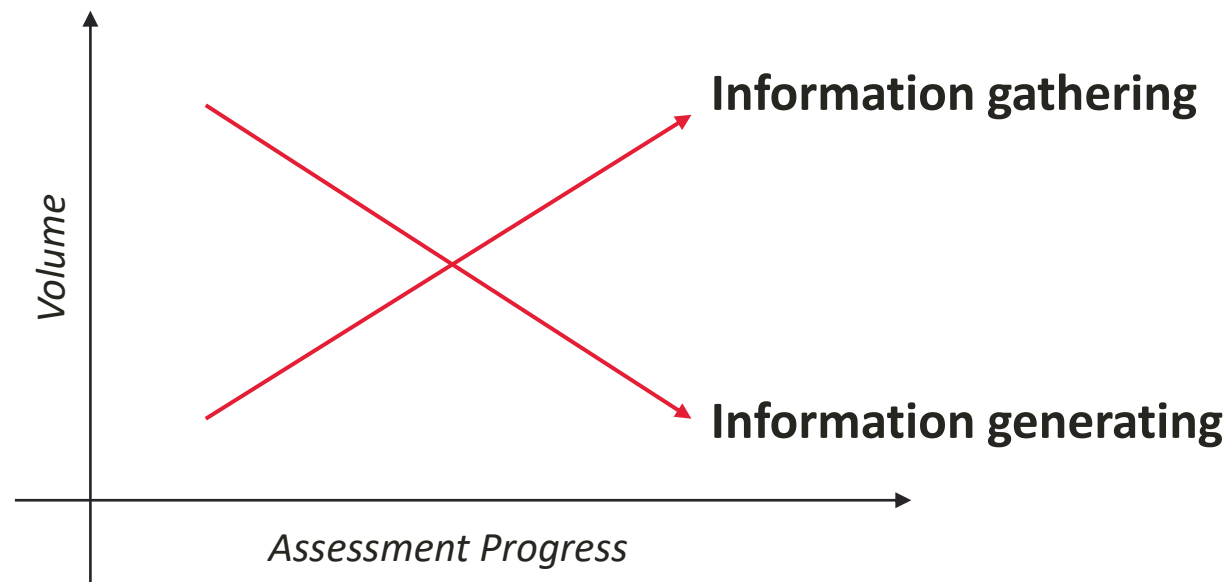
C-3PO—Manufacturer: Cystol Galactic (remanufactured from original components)
 • Make: Class three protocol droid • Height: 1.7 m (5 ft 6 in)
 • Weight: 75 kg (165 lbs) • Primary function: Diplomacy, translation, and utility • Homeworld: Unknown

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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*

INTERNATIONAL STANDARD

ISO 10993-1:2018(E)

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.

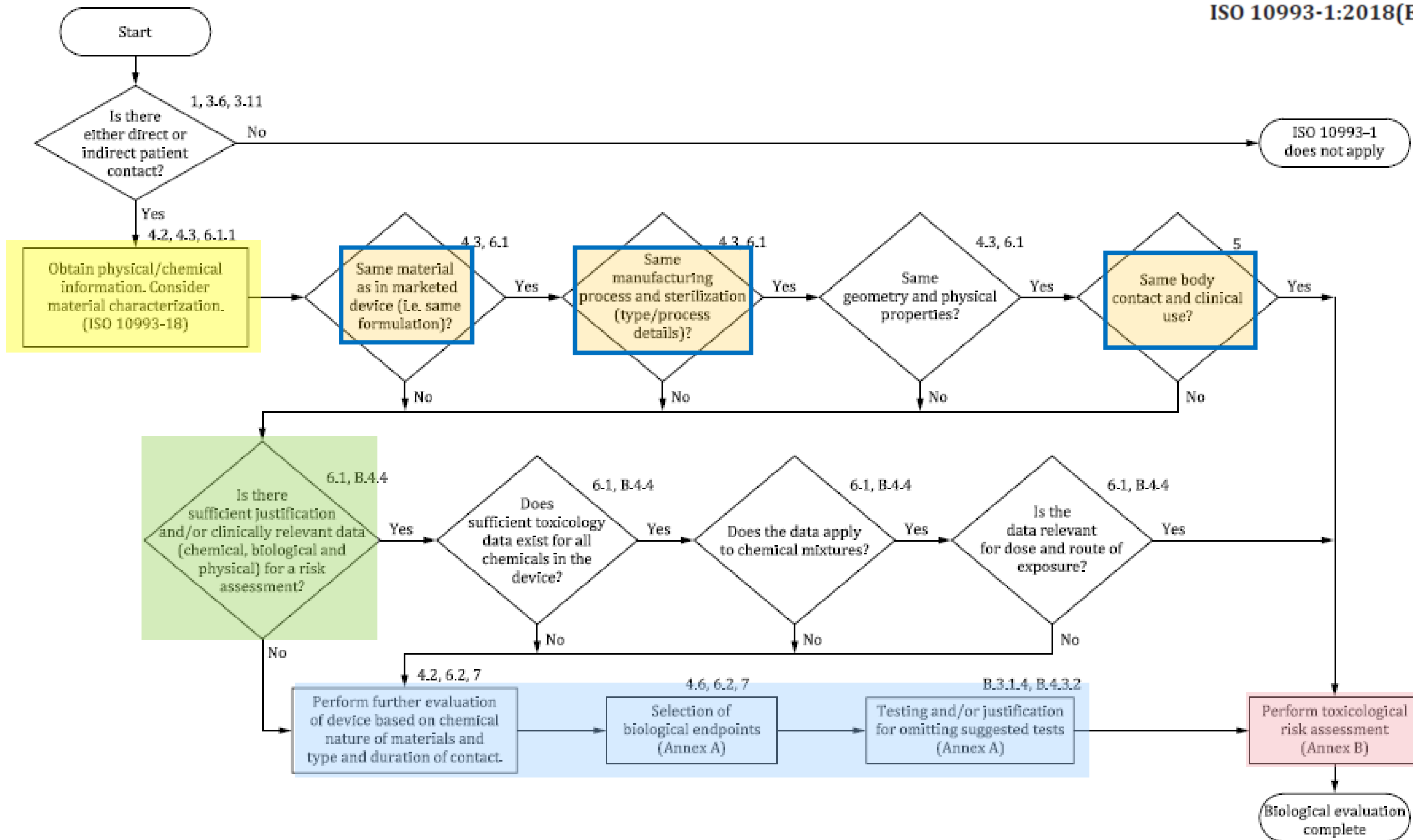


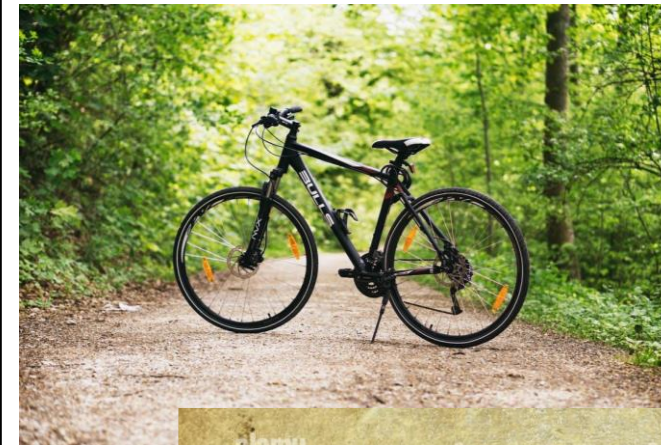
Figure 1 — Summary of the systematic approach to a biological evaluation of medical devices as part of a risk management process

Medical device categorization by

Nature of body contact

Contact duration

Magnitude, duration, & freq.

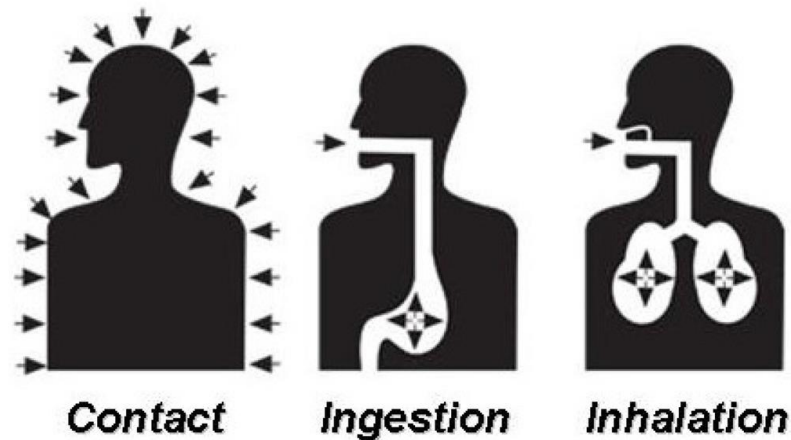


THE DOSE MAKES THE POISON.



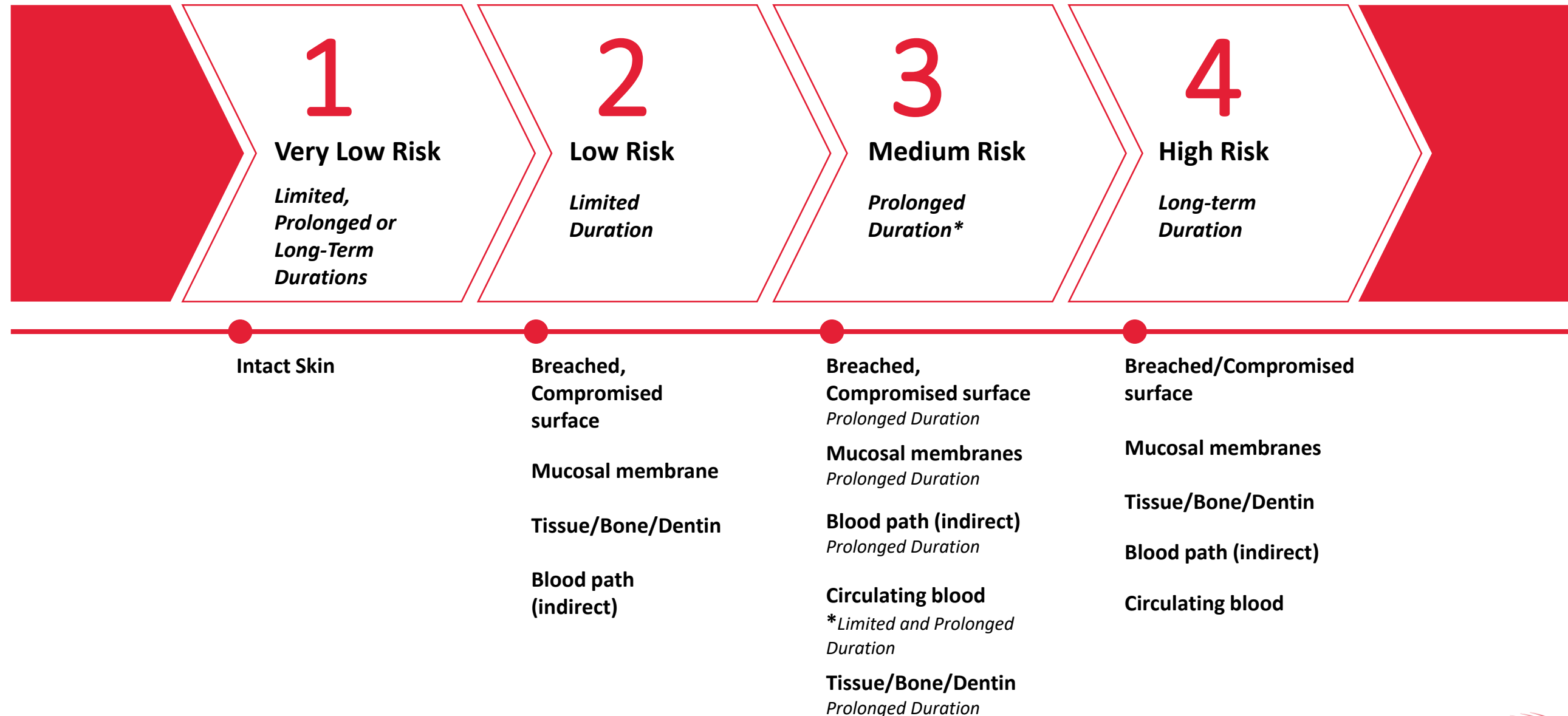
Medical device categorization by		
Nature of body contact		Contact duration
Category	Contact	A - limited (≤24 h)
		B - prolonged (>24 h to 30 d)
Surface medical device	Intact skin	C - Long term (>30 d)
		A
		B
	Mucosal membrane	C
		A
		B
	Breached or compromised surface	C
		A
		B

Varying routes through which exposure can occur.



• Device Risk Categories

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



VERY LOW RISK | RISK LEVEL 1

Intact Skin

Limited, Prolonged or Long-Term Duration

Examples

- Electrodes
- Fixation tapes
- Compression bandages

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

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	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	
Category	Contact	A - limited (≤24 h) B - prolonged (>24 h to 30 d) C - Long term (>30 d)																
Surface medical device	Intact skin	A	X ^a	E ^b	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			

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*

**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 immunoabsorbents.

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*

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 immunoabsorbents.

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) ←

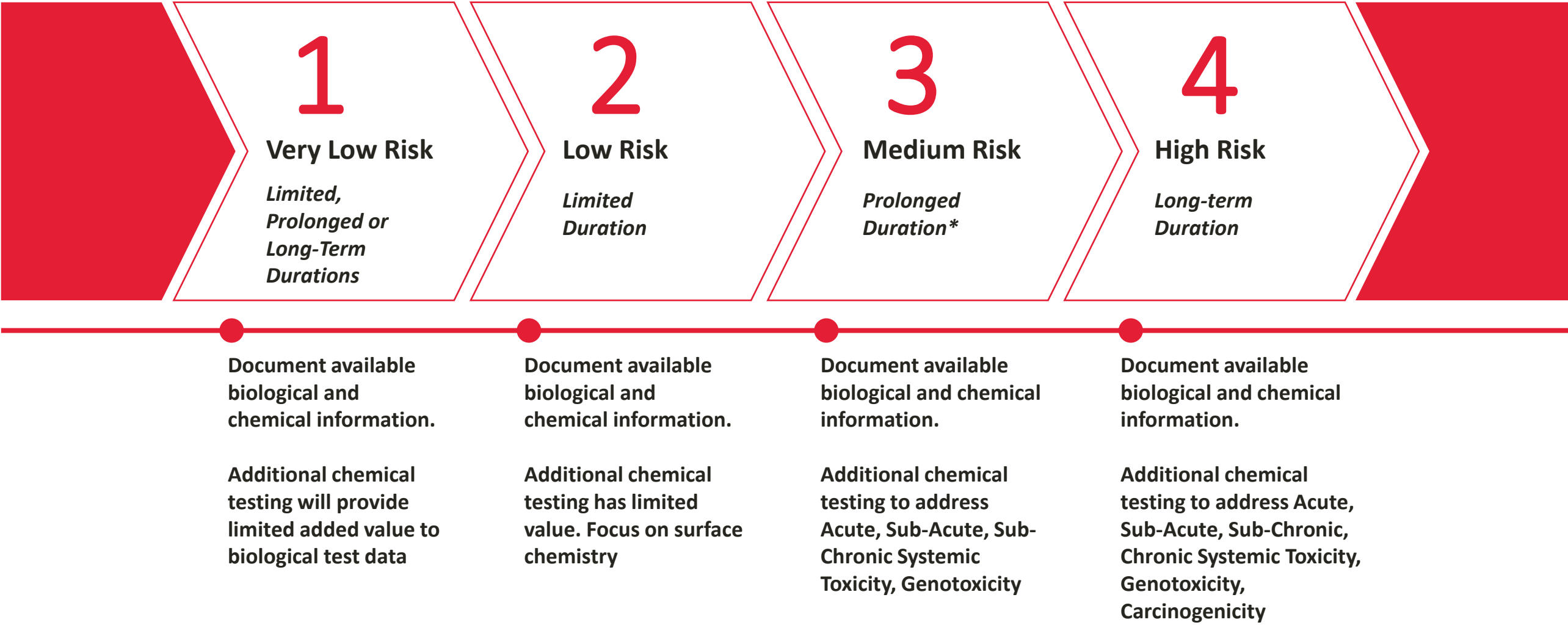
Consider duration of device exposure to Patient when determining extraction conditions
- Exaggerated
 - single use devices used for less than 24h, where repeat use of a new device each day would result in categorization as prolonged or long-term contact;
 - single use devices used for several days, where 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

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

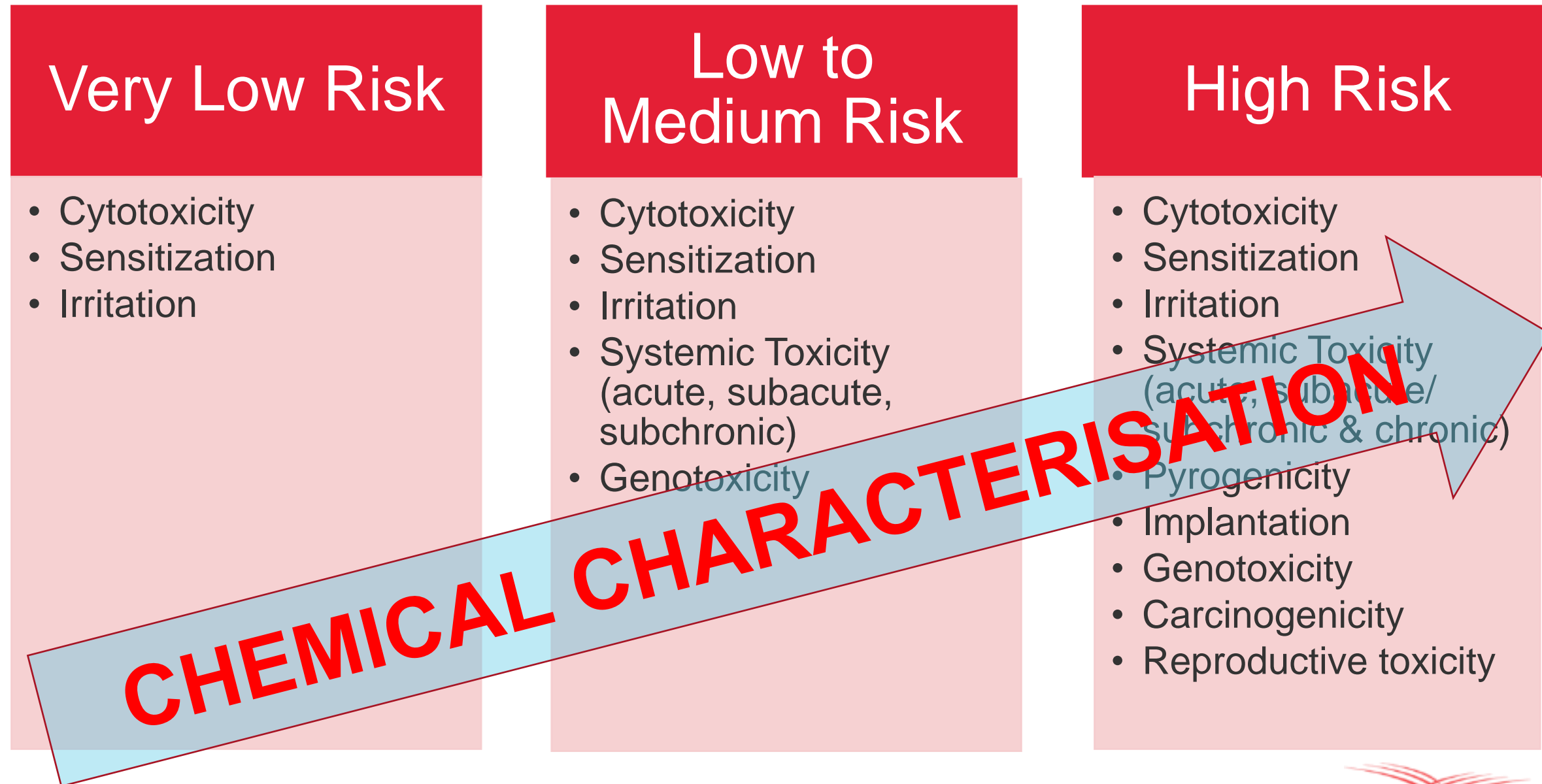
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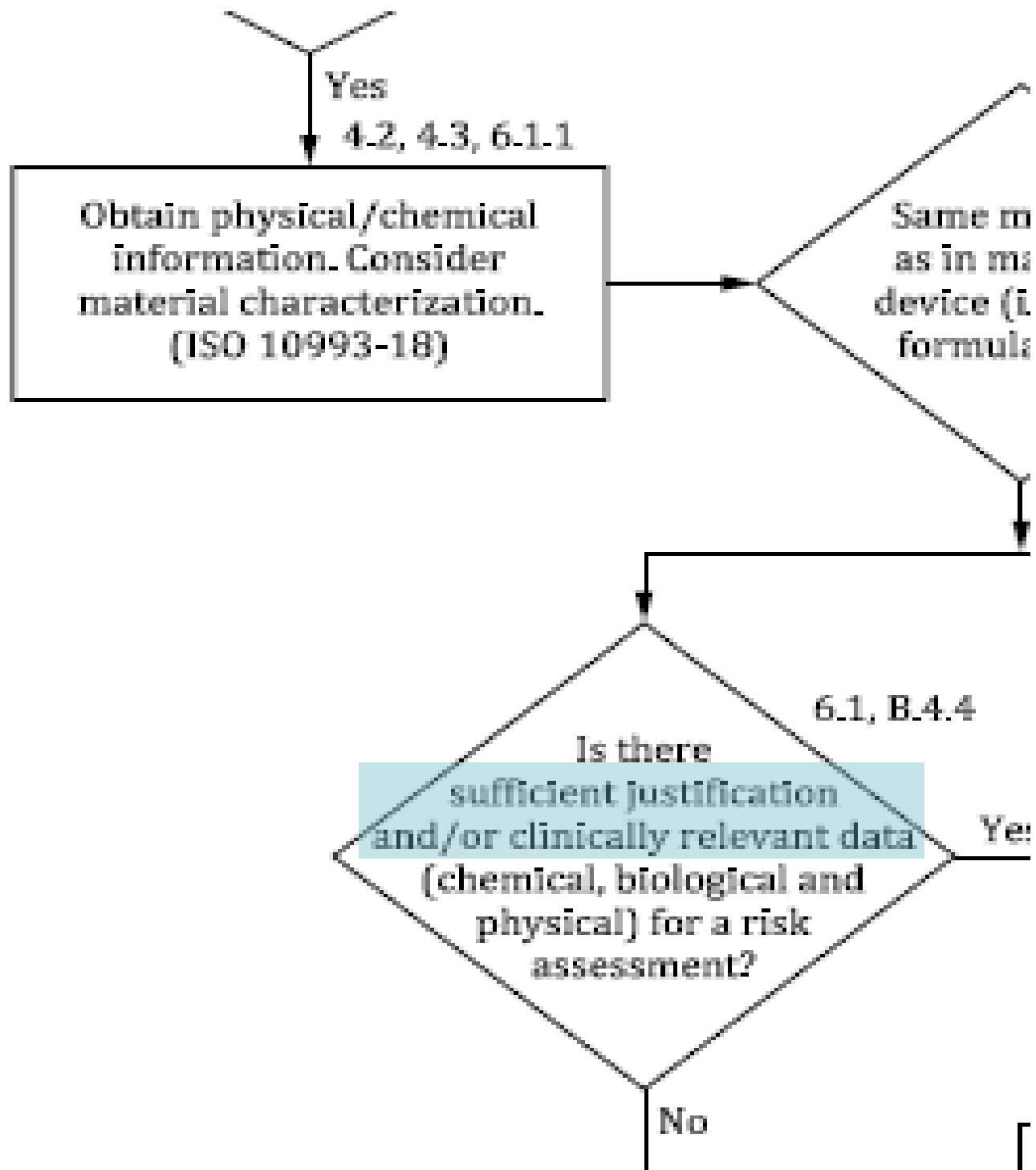


Focus on adequately protective:

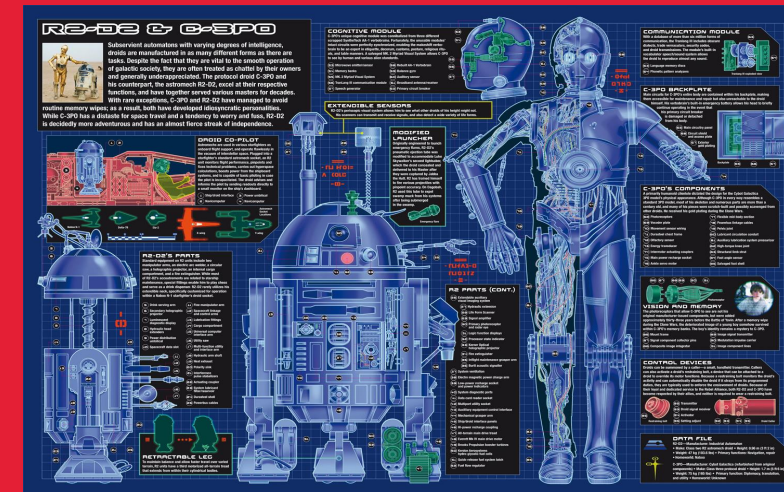


Biological Evaluation at varying risk levels – Assessing Endpoints through levels of Chemical Characterization





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 <u>MAY</u> be adequate <i>(consider material science and clinical use)</i>
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

John Iannone

Global Head of Biocompatibility, Toxicology, Chemistry, Sterility, Microbiology – QRA