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UPDATE: ISO CD 10993-1 and FDA Guidance

WHAT IS PROPOSED AND POSSIBLE DIRECTION

NICHOLAS CHRISTIANO

04 FEB 2025

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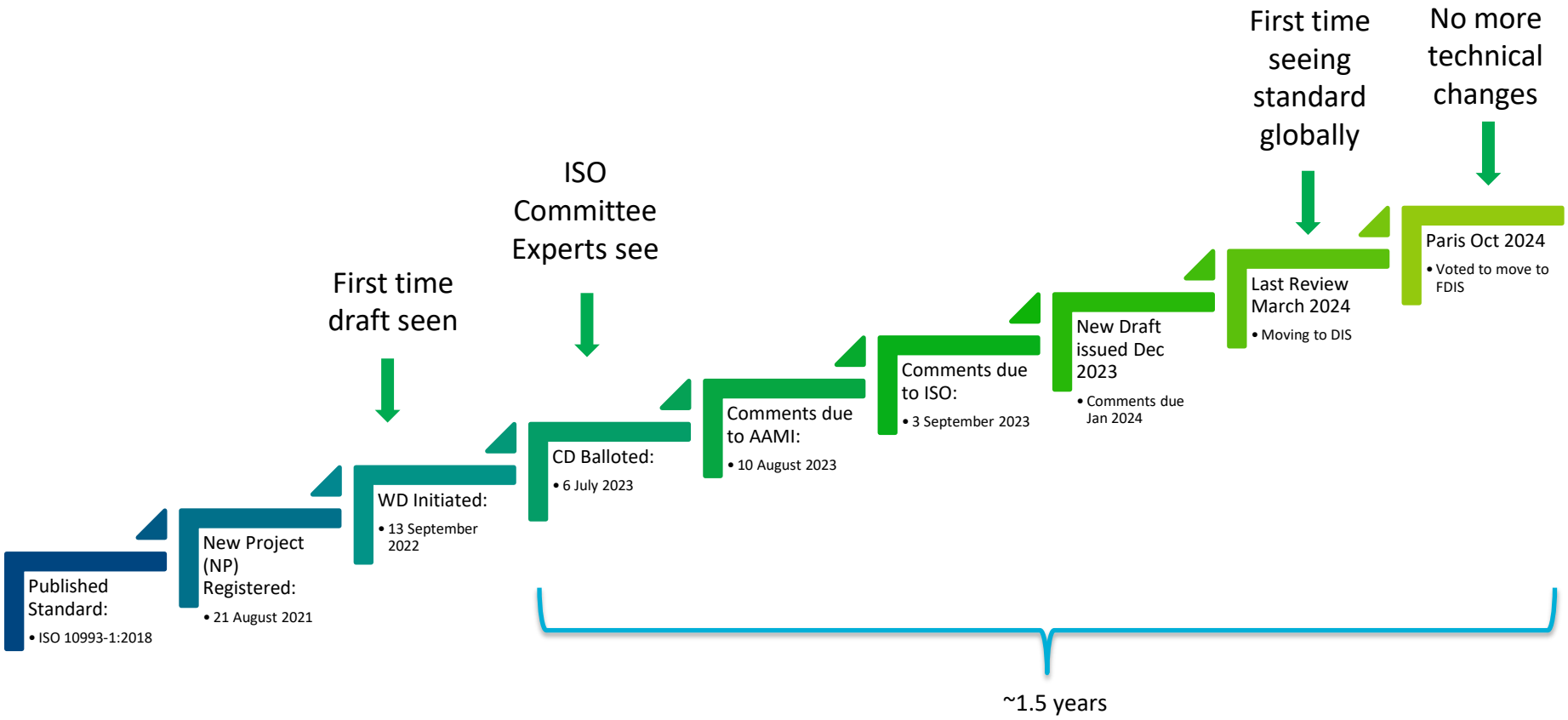
How did we get here?



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What was in the FDIS?

HOW DID THE US VOTE?

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2

The results from the 2021 New Work Item ballot

- 397 total comments (231 from US)

Answers to Q.1: "Do you agree to start a revision of ISO 10993-1?"		
22 x	Yes	Australia (SA) Bahrain (BTMD) Belgium (NBN) Brazil (ABNT) China (SAC) Denmark (DS) France (AFNOR) Ireland (NSAI) Italy (UNI) Japan (JISC) Korea, Republic (Malaysia (DSM) Netherlands (NEN) Norway (SN) Russian Federation (GOST R) Saudi Arabia (SASO) Spain (UNE) Sweden (SIS) Switzerland (SNV) Tanzania, United Republic of (TBS) Thailand (TISI) United Kingdom (BSI)
2 x	No	Germany (DIN) United States (ANSI)
7 x	Abstain	Argentina (IRAM) Austria (ASI) India (BIS) Iran, Islamic Republic of (INSO) Israel (SII) Portugal (IPQ) Singapore (SSC)

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What was in the 2021 New Work Item Proposal?

What is in the Currently Balloted Committee Draft (CD)?

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4

2023 CD 10993-1: New Outline

Introduction vi

1 Scope 1

2 Normative references 1

3 Terms and definitions 2

4 General requirements for biological evaluation process 6

4.1 Biological evaluation within an ISO 14971 Risk management framework 6

4.2 Biological Evaluation Plan 8

5 Biological evaluation process 8

5.1 Overview 8

5.2 Product life cycle 10

5.3 Animal Welfare 10

6 Biological risk analysis 10

6.1 Staged Approach 10

6.2 Categorization of medical device and determination of scope of evaluation 10

6.2.1 Exposure duration 11

6.2.2 Body contact and biological effects for consideration 12

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2023 CD 10993-1: New Outline

6.3 Consideration of identified biological effects 16
6.3.1 Overall approach 16
6.3.2 Cytotoxicity 17
6.3.3 Irritation 17
6.3.4 Sensitization 17
6.3.5 Systemic Toxicity 17
6.3.6 Local Effects after Implantation 18
6.3.7 Genotoxicity 18
6.3.8 Carcinogenicity 19
6.3.9 Materials Mediated Pyrogenicity 19
6.3.10 Haemocompatibility 19
6.3.11 Other biological effects 19
6.3.12 Other Factors to be considered 20
6.4 Identification of characteristics related to biological safety 21
6.5 Identification of biological hazards, hazardous situations, and harm 22
6.6 Biological Equivalence 23
6.6.1 Clinically established material or medical device 25
6.7 Gap analysis 26

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2023 CD 10993-1: New Outline

6.8 Supplementary testing 26
6.8.1 General requirements 26
6.8.2 Biological, Physical and Chemical Testing 27
6.8.3 Degradation Testing 27
6.8.4 Toxicokinetic Studies 28
6.9 Risk estimation 29
7 Risk evaluation 29
8 Risk Control 30
9 Biological evaluation report 30
10 Production and Post-production activities 30
Annex A (informative) Guidance on the conduct of biological evaluation within a risk management process 32
Bibliography 45

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Added the concept of:

- User's body just not Patients
  - *Point of care, at home, etc.*
- Chemical and physical effects
- Evaluating significant changes through lifecycle that could impact biocompatibility
  - *Metals vs. Biodegradables*
  - *What testing will be referenced? TBD*
- Specifically calls out that documentation can be used from supported clinical evaluations
  - *Line extensions, changes, etc.*
- Removes infection agents from the scope

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Also:

- Sensitive Populations
  - *More emphasis placed here*
- No specific systemic toxicity
  - *Justify: Acute/Sub-acute Sub-chronic/chronic*
- Hard fought discussion on Foreseeable misuse
  - *Length of time, indication, etc.*
- If you have a risk of systemic toxicity, then you must assess genotoxicity
- Increasing amount of presence of the chemical and physical effects

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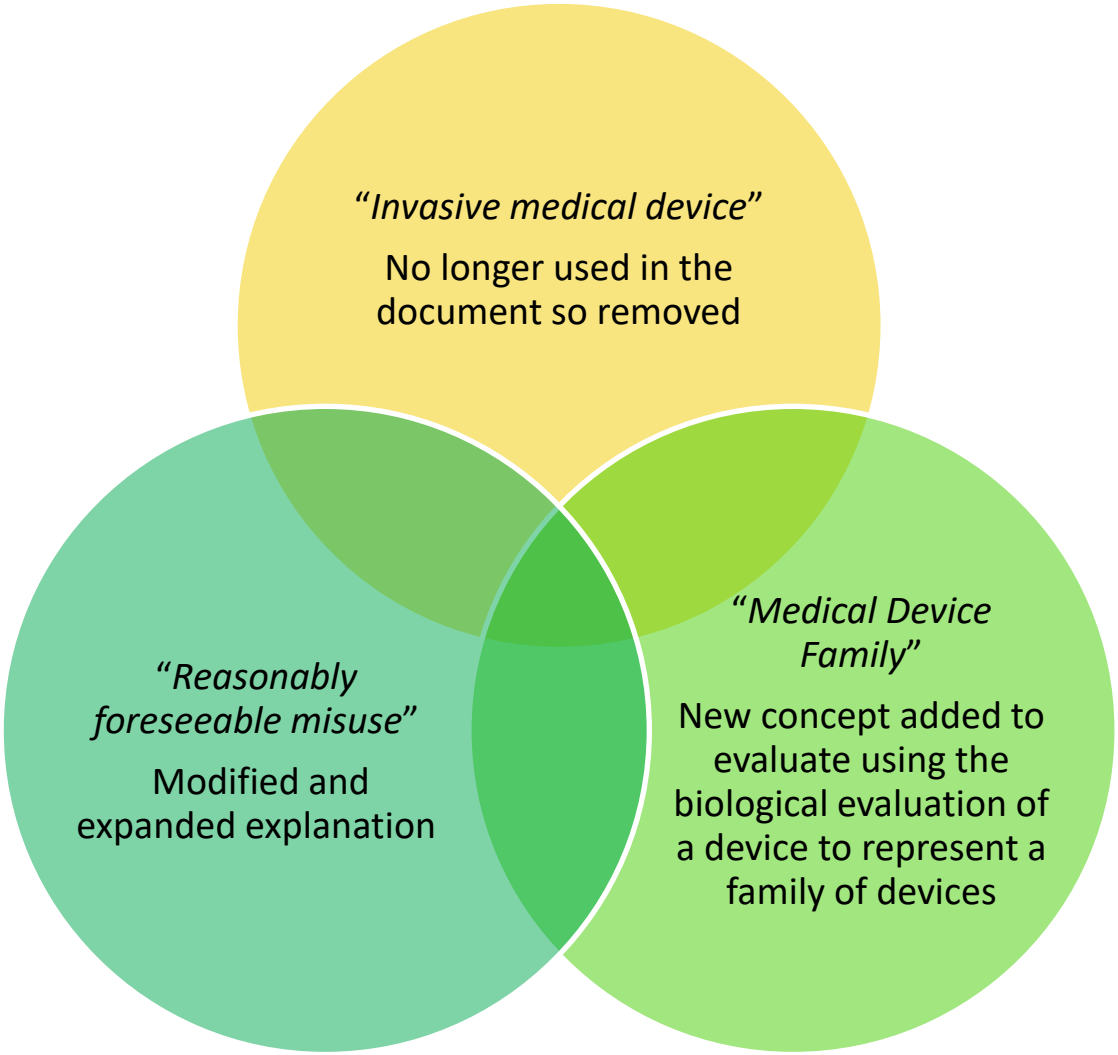
Terms and definitions



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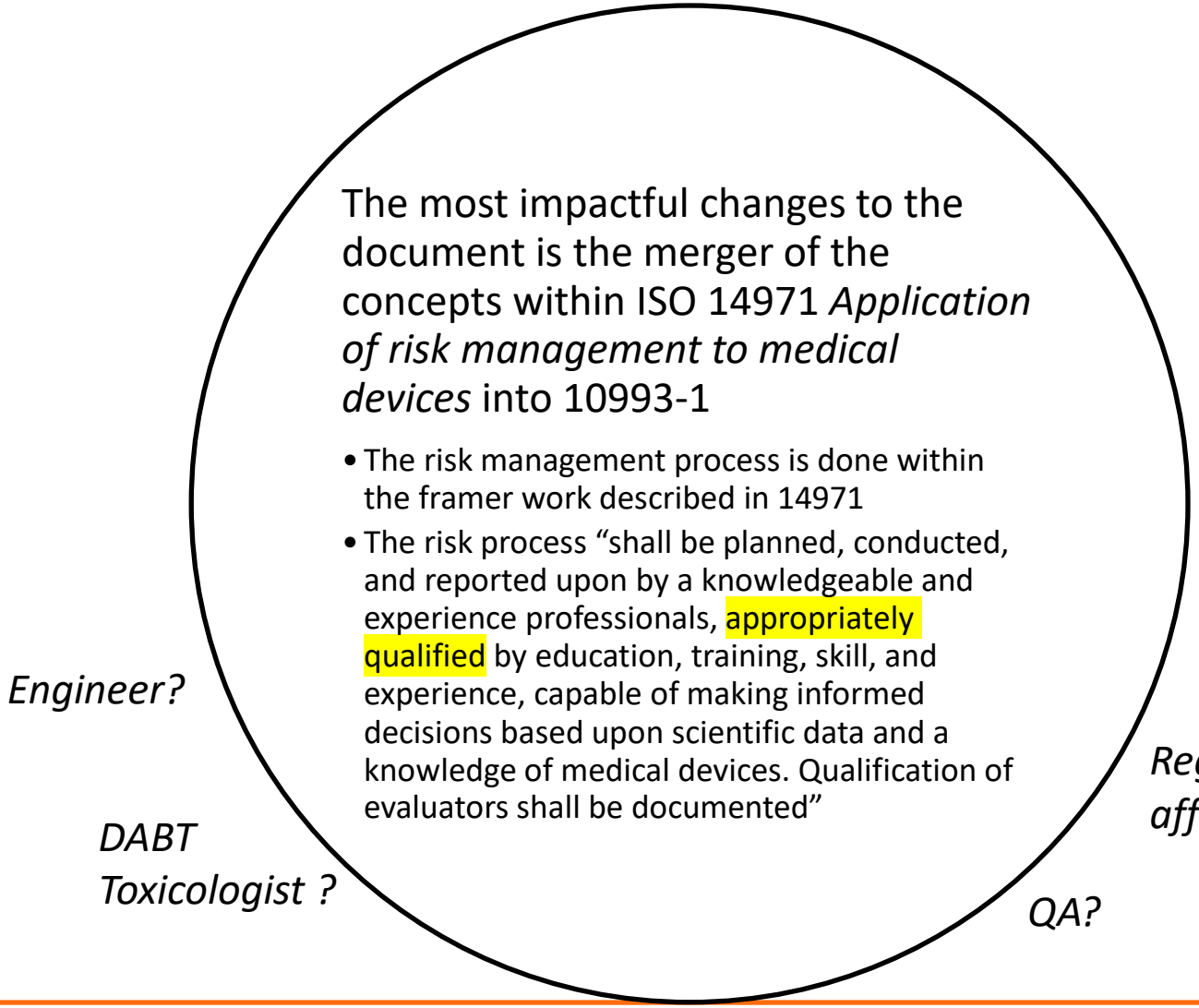
ISO 14971 and ISO 10993-1



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ISO 14971 and *now* ISO 10993-1

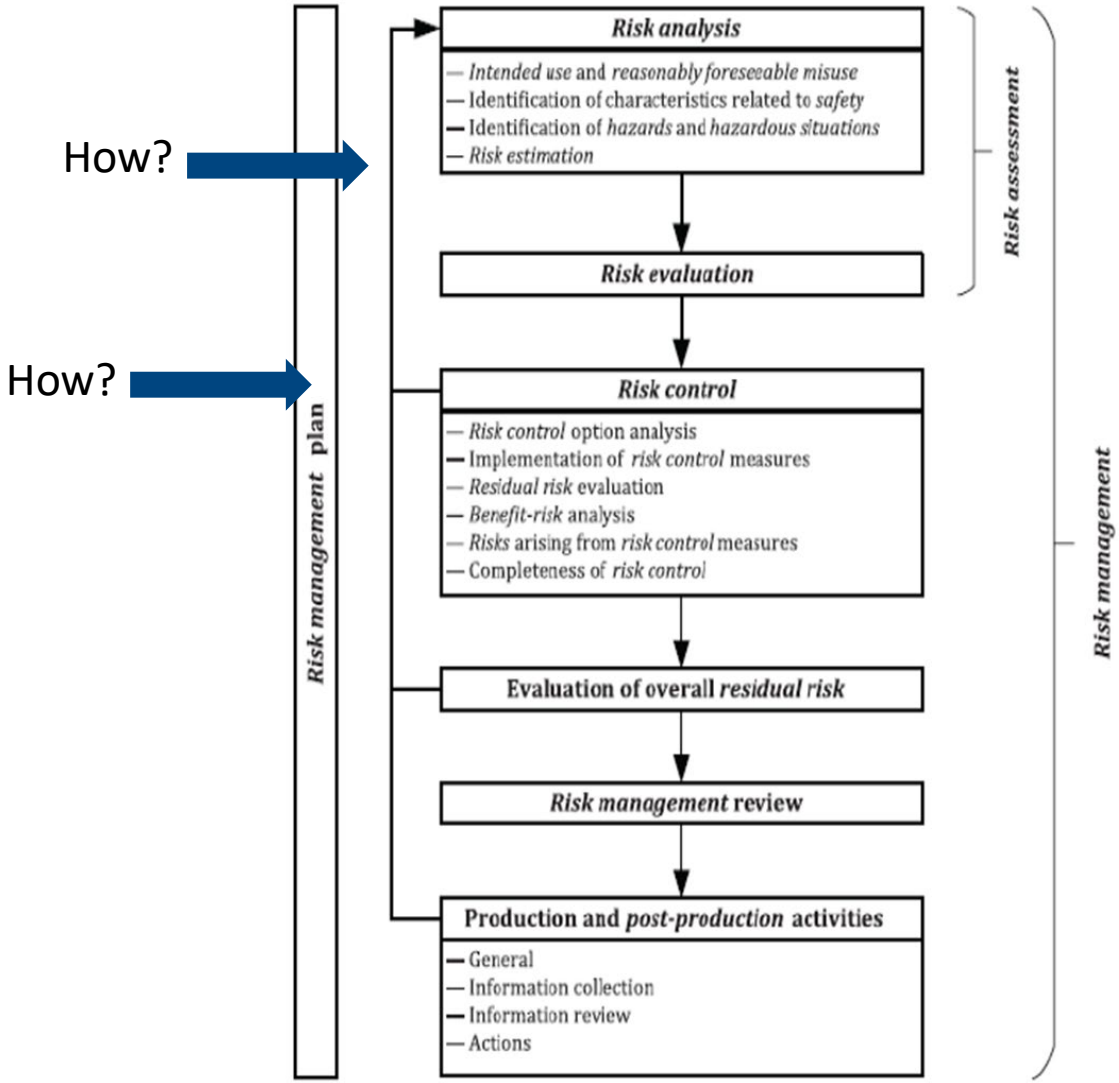

Figure 1 — ISO 14971 Risk Management Framework

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ISO 14971 and ISO 10993-1

Risk analysis requires

- Description and categorization of medical device including
  - Composition
  - Physical form
  - Body contact during use (including foreseeable misuse)
- Identification of possible biological effects

Risk estimation (probability and severity of harm)

- Evaluates information of materials and processes regarding the risk of potential hazardous effects
- If existing data are insufficient, further physical/chemical or biological testing can be required to estimate risks

Risk evaluation

- The acceptability or otherwise estimated biological risks

Risk control

- Actions taken to mitigate known risks
- Applied in the following order
  - Design or manufacturing change
  - Implementation of protective measures
  - Provision of information or training
- Re-analysis of risks (including retesting) can be necessary to confirm that no unacceptable new risks have been introduced by implementing measures

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New guidance on Biological Evaluation Plans (BEPs)

Needs to be a “written” plan and *shall* identify (at a minimum)

- The strategy and planned content of the biological evaluation based on the review of existing data and any additional device characterization or testing
- Definition of criteria to determine the actability of risk associated with the purpose of the medical device (or foreseeable misuse)
- Definition for determining the acceptability of the risk associated with the device (or foreseeable misuse)
- The planned activities for evaluations the biological risk
- The aspects of the evaluation requiring specific technical competencies (i.e., tox assessment by a board-certified toxicologist)
- The person responsible for the biological evaluation and CV

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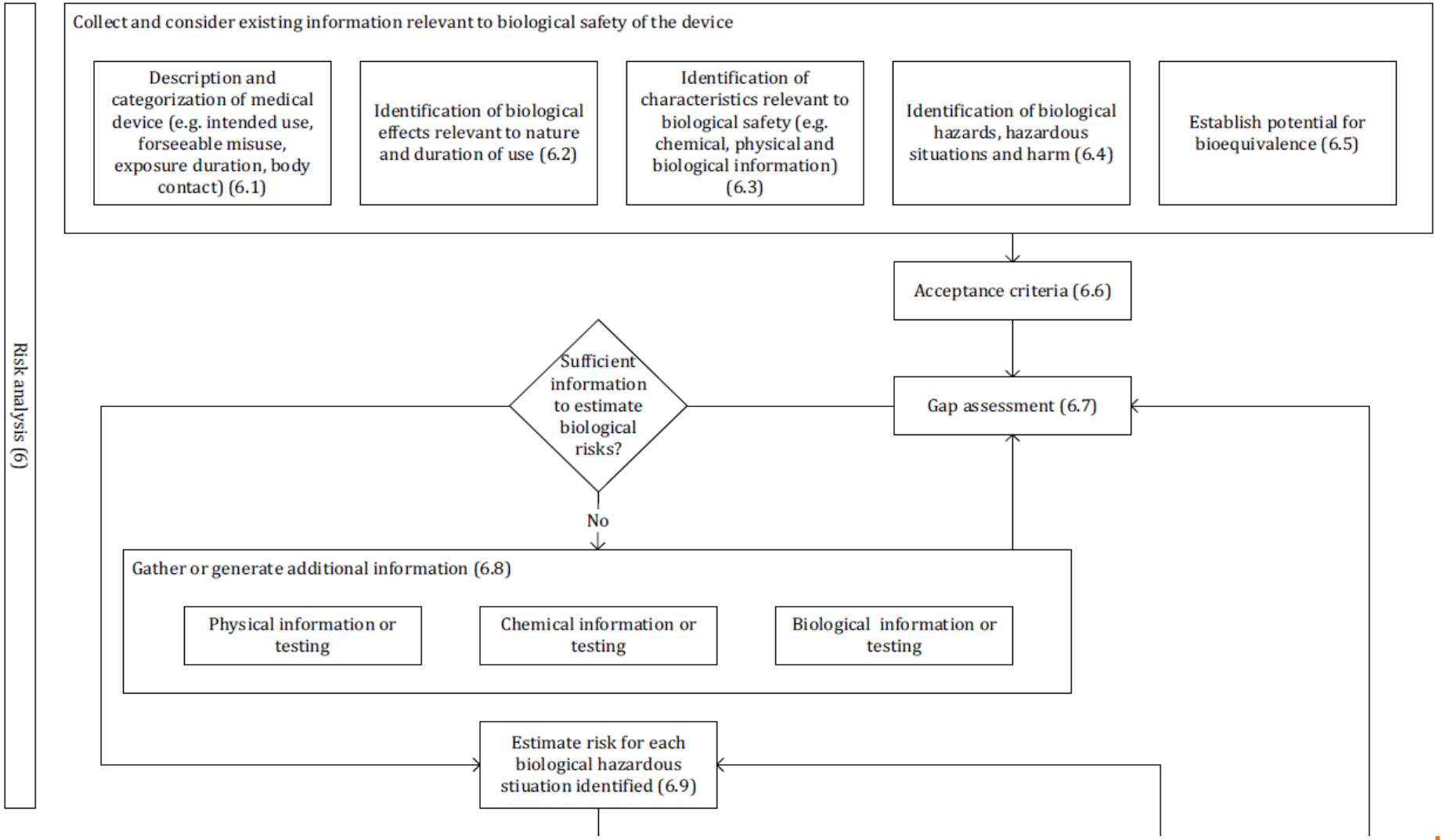
The biological evaluation process (BEP)



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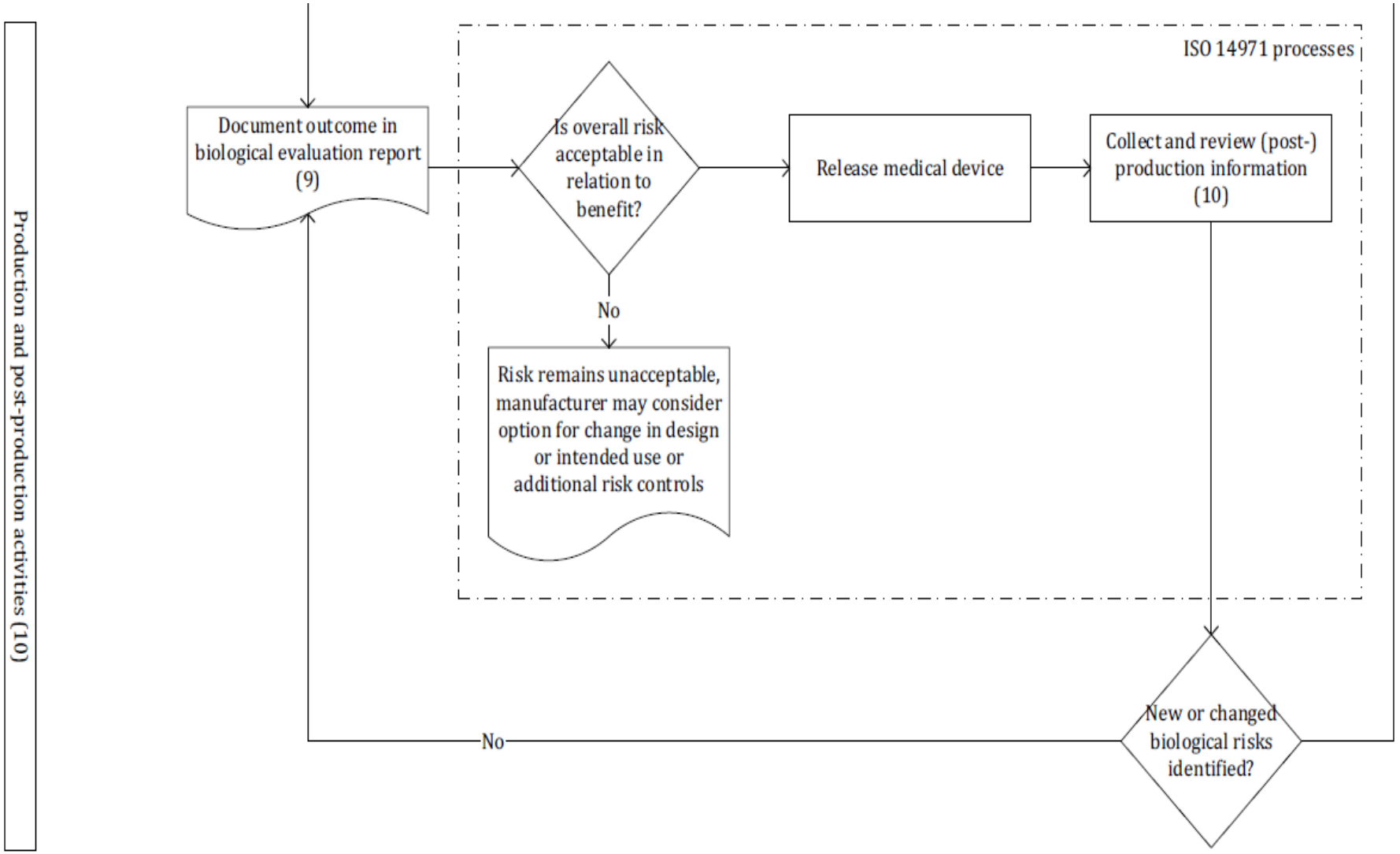
The biological evaluation process (BEP) Continued



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Shall be evaluated over the "whole life cycle" of the device

- Chemical or physical degradation
- Physical failures that might expose new materials
  - *Polymers may break down*
- If the biological safety is "different to that anticipated" during development
- For re-usable devices, biological safety "*shall* be evaluated for the maximum number of validated processing cycles"
  - *Detergent build up, corrosion, etc.*

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Animal Welfare

Overall goal is to “minimize to that which is strictly necessary to complete the biological evaluation.

- Consider the 3Rs (Reduce, Replace, Refine)

“A justification shall be documented for all animal tests conducted”

- In vivo testing “shall **not** be carried out where”:
  - Results are available from relevant studies that have been carried our previously
  - The existing non-clinical and clinical data demonstrate safety for the intended use therefore “animal testing would be unethical”

Reduced verbiage on need, now just references part 2
This did NOT get included

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Exposure duration

More guidance on devices with multiple contacts (i.e., iv bags or urinary catheters)

- "with expected or intended multiple exposures to a device, the duration category shall be based on the **total exposure period** of a single patient
- The total exposure period definition:
  - The period in days between first and last use of the medical device or accessory or a replacement of the same device.
  - This means that a device might only have 5 min contact a day but is in contact every day for a week
  - The contact duration is **not** 35 min (5 min x 7) but shall be considered 7-day contact
- If it has "infrequent use" then the total exposure period is determined for a single treatment
- Devices that have "very brief contact" with the body, "typically for less than one minute" it may be possible to prepare a written justification

Historical
- Sum of total contact

Revised
- Any contact >1min defaults to 24 hours

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Cumulative use:

- For repeated uses over a period, you must assess bioaccumulation. If you don't expect bioaccumulation, then a new device after a period would be a new exposure. "Proposed alternative wording
  - However, when calculating the total exposure duration, the potential for bioaccumulation of medical device constituents (e.g. per- and polyfluoroalkyl substances) shall be considered. Where bioaccumulation is expected, the contact duration shall be long-term unless otherwise justified
  - Where risk for bioaccumulation is identified during subsequent biological evaluation of the medical device the contact duration shall be long-term unless otherwise justified."

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Insignificant risk skin contacting medical devices

- Medical devices that only contact intact skin during normal handling
  - Wearables, sensors, etc.
- Or skin contacting components are made from materials in common use for consumer products

Are considered to have "**no significant biological risks**" and can do a "**simple written justification**"

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Overall concept changes

- Instead of “endpoints for a biological evaluation” the endpoints are called “Biological Effect”
- Look at the entire data set before using charts
- You might need to consider additional or fewer biological effects that in the chart
- There are specific circumstances which require considerations of other effects (6.3.11 and 6.3.12)
  - Immunotoxicity
  - Neurotoxicity

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6.2.2.2.3 Mucosal Contacting Medical Devices

These are surface-contacting medical devices having contact with mucosal membranes.

EXAMPLES: Contact lenses, urinary catheters, intravaginal and intra-intestinal devices (stomach tubes, sigmoidoscopes, colonoscopes, gastroscopes), endotracheal tubes, bronchoscopes, some dental prostheses and orthodontic devices

For these medical devices, the following biological effects listed in Table 2 shall be considered.

Table 2 — Biological effects to be considered for devices in contact with mucosal membranes

Duration	Biological Effect[1, 2, 3]											
					Systemic Toxicity							
	Cytotoxicity	Sensitization	Irritation	Material Mediated Pyrogenicity	Acute	Sub-Acute	Sub-Chronic	Chronic	Effects after Implantation	Genotoxicity	Carcinogenicity	Hemocompatibility
A – limited (≤ 24 h)	E	E	E									
B – prolonged (24 h to 30 d)	E	E	E	E	E	E			E	E		
C – long-term (> 30 d)	E	E	E	E	E	E	E	E	E	E	E	

E = Biological effects to be evaluated.

[1] It is important to emphasize that identification of an effect for evaluation requires consideration of existing

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New charts

Table 3 — Biological effects to be considered for devices in contact with blood

Duration	Biological Effect[1, 2, 3]											
					Systemic Toxicity							
	Cytotoxicity	Sensitization	Irritation	Material Mediated Pyrogenicity	Acute	Sub-Acute	Sub-Chronic	Chronic	Effects after Implantation	Genotoxicity	Carcinogenicity	Hemocompatibility
A – limited (≤ 24 h)	E	E	E	E	E					E[4]		E
B – prolonged (24 h to 30 d)	E	E	E	E	E	E			E[5]	E		E
C – long-term (> 30 d)	E	E	E	E	E	E	E	E	E[5]	E	E	E

E = Biological effects to be evaluated.

[1] It is important to emphasize that identification of an effect for evaluation requires consideration of existing data sets first and only if these are insufficient for risk assessment should additional testing be considered. This table is not a checklist for testing. (see 6.3)

[2] For some medical devices it may be appropriate to consider evaluation of additional or fewer biological effects than indicated in this table. 6.3.11 provides guidance on circumstances which may require modifications in the approach to biological evaluation.

[3] In addition to the specific biological effects identified in this table, it is important to consider if there are specific circumstances which require consideration of other effects (see 6.3.11) or additional factors (see 6.3.12).

[4] Only considered for devices having direct contact with circulating blood (see 6.2.2.2.4).

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New Chart

For these medical devices, the following biological effects listed in Table 4 shall be considered.

Table 4 — Biological effects to be considered for devices with other tissue contact

Duration	Biological Effect[1, 2, 3]											
					Systemic Toxicity							
	Cytotoxicity	Sensitization	Irritation	Material Mediated Pyrogenicity	Acute	Sub-Acute	Sub-Chronic	Chronic	Effects after Implantation	Genotoxicity	Carcinogenicity	Hemocompatibility
A – limited (≤ 24 h)	E	E	E	E	E							
B – prolonged (24 h to 30 d)	E	E	E	E	E	E			E	E		
C – long-term (> 30 d)	E	E	E	E	E	E	E	E	E	E	E	

E = Biological effects to be evaluated.

[1] It is important to emphasize that identification of an effect for evaluation requires consideration of existing data sets first and only if these are insufficient for risk assessment should additional testing be considered. This table is not a checklist for testing. (see 6.3)

[2] For some medical devices it may be appropriate to consider evaluation of additional or fewer biological effects than indicated in this table. 6.3.11 provides guidance on circumstances which may require modifications in the approach to biological evaluation.

[3] In addition to the specific biological effects identified in this table, it is important to consider if there are specific circumstances which require consideration of other effects (see 6.3.11) or additional factors (see 6.3.12).

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Consideration of Identified Effects

For each medical device “all biological effects” that are identified shall be addressed (justified and documented) in the risk assessment

- You use tables 1,2,3, and 4 as a framework to identify the biological effects
- You then decide if each effect is mitigated based of information or if additional testing is required

The identification of these effects establishes your criteria for risk acceptability. Factors to consider and document in your BEP are:

- Required absence of or maximum severity
- Frequency of an effect
- Outcomes of the testing

The identified biological effects:

- Cytotoxicity
- Irritation
- Sensitization
- Systemic toxicity
- Genotoxicity
- Carcinogenicity
- Material mediated pyrogenicity
- Hemocompatibility
- Other possible effects to consider
  - Immunotoxicity
  - Neurotoxicity
  - Reproductive and developmental toxicity

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Addition effects that might need to be considered

Consideration of external factors

- High levels of absorption through the skin
- Material degradation
- Particulates
- Toxicokinetics
- Presence of specific substances of concern
  - Metals that might release certain ions (cobalt)
  - Processing agents that might pose a risk to the patient (grinding, blasting, surface impacts)
  - Ethylene oxide
  - Change in minor components (colorants)
  - Final cleaning processes
  - Any substance with a toxicologically derived margin of safety (MOS) of less than 1
  - Residuals from process changes.

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Endpoint specific considerations

Cytotoxicity, irritation, sensitization

- All medical devices having direct or indirect contact with body irrespective of nature of that conduct, shall be evaluated

Systemic Toxicity

- Not usually required for medical devices that:
  - In contact with intact skin
  - Limited duration contact with mucosal tissues
- All other body contacts shall e evaluated for acute systemic toxicity
  - Prolonged shall be evaluated for sub-acute
  - Long term shall be evaluated for sub-acute, sub-chronic, and chronic
  - Comprehensive implant assessments might provide the necessary info for all systemic endpoints, including reproductive toxicity

Genotoxicity

- Not usually required for:
  - Contact with intact skin
  - **Limited contact with tissues, other then circulating blood**
- **Shall be evaluated for:**
  - Prolong or long term with tissues, **other than blood**
  - Long term mucosal or compromised surfaces
  - Longer indirect contact with circulating blood,
  - **Direct contact with circulating blood for any duration**

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Endpoint specific considerations

- Carcinogenicity
  - Not required for:
    - Intact, compromised, or mucosal contacts
  - Shall be evaluated
    - Long term contact with any other tissues
  - It is “rare” for testing to be done, more appropriate is a robust evaluation of carcinogenicity including:
    - E&L data with toxicological risk assessment
    - Review of materials and processes
- Material mediated pyrogenicity
  - Chemically induced pyrogenicity is rare and only occurs in small number of substances rarely seen in medical devices
    - Unless unknown materials
    - In many cases it could be sufficient to present a rational that the composition of the final medical device does not present a risk of pyrogenicity
- Hemocompatibility
  - Devices that have direct or indirect contact with circulating blood s(regardless of duration) and shall be evaluated for hemocompatibility
  - Understanding the relevant physical characteristics is very important

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Biological Equivalence

A new key concept is considering existing data to demonstrate a new or change product shows biological equivalence

- If you can demonstrate equivalent:
  - Materials
  - Processing
  - Location of use in the body
  - Chemical comparison

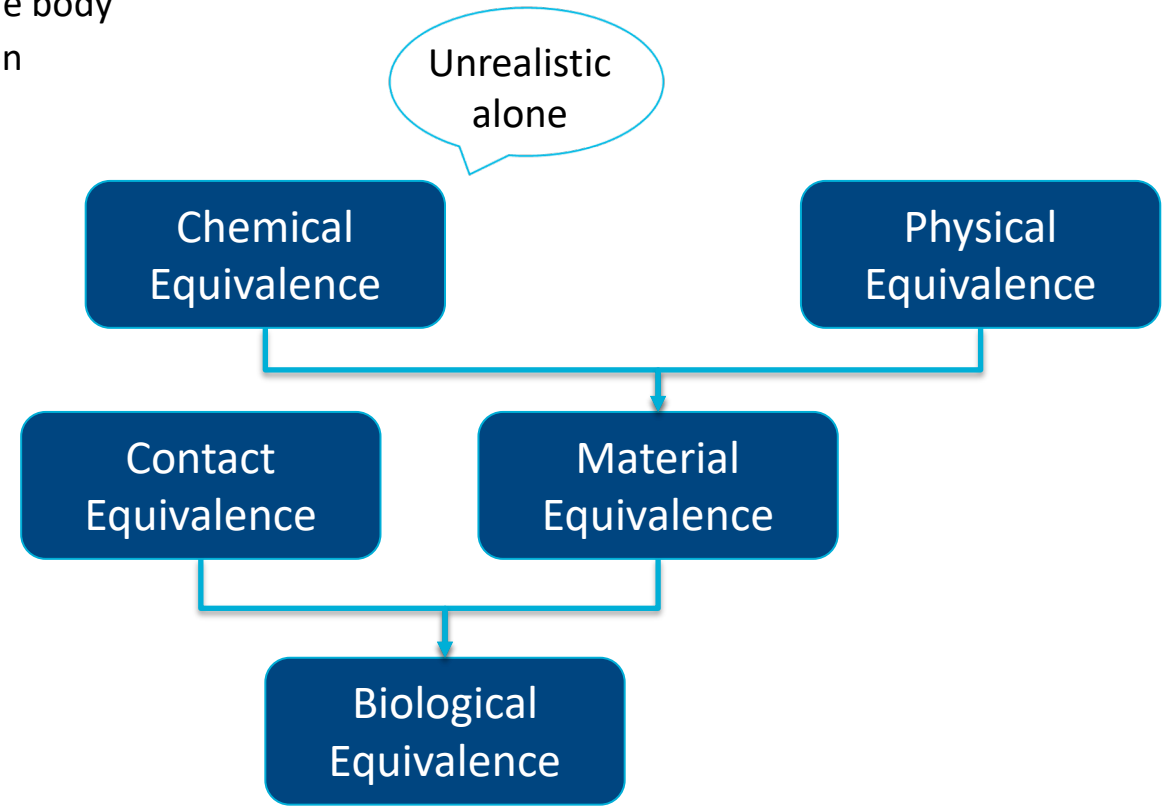

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Figure 4 — Biological equivalence process map

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Added clinical established data – Post market data

If you have a device that has an established, extensive clinal use in a relevant contact category and:

- There is sufficient evidence to support biosafety
- You can establish biological equivalence

You can extrapolate the conclusions of the BEP to the clinically established material or medical device

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What about the Annexes?

CD Annex A: guidance on the conduct of biological evaluation within a risk management process

- Previously was Annex B
- Some content moved to main body
- Still being evaluated to see if things should be removed or deleted based on main text

ISO 10093-1:2018

- Annex A: revised and moved into main body as Tables 1,2,3,and 4
- Annex B: (above)
- Annex C: Literature review- removed
- Bibliography, will be revised at the end of the CD process

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New FDA Guidance

APPENDIX

What is in the Currently Balloted Committee Draft (CD)?

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34

The Nice List

Synthetic Polymers	Acrylonitrile butadiene styrene (ABS)
	Cured epoxy adhesives
	Fluoropolymers including polytetrafluoroethylene (PTFE), expanded polytetrafluoroethylene (ePTFE), polyvinylidene fluoride (PVDF), and fluorinated ethylene propylene (FEP);
	High impact polystyrene (HIPS)
	Polyamides, including nylon
	Polybutylene terephthalate (PBT)
	Polycarbonate (PC)
	Polyetheretherketone (PEEK)
	Polyether imide (PEI)
	Polyethylenes, including low-density polyethylene (LDPE) and high-density polyethylene (HDPE)
	Polyethylene terephthalate (PET)
	Polymethylmethacrylate (PMMA)
	Polyoxymethylene (POM)
	Polyphenolsulfone (PPSU)
	Polypropylene (PP)
	Polyurethane (PU)
	Silicone
Fabrics	Polyurethane fabrics, including Lycra
	Cotton fabrics
	Polyamide fabrics, including nylon
	Silk fabrics

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The Naughty List

Medical Device Characteristic	Reason
Materials not in the nice list or novel materials and bulk metals (e.g., titanium, stainless steel, nitinol, gold)	There are known risks, or FDA does not have adequate experience with these materials that may introduce toxicity risks.
Stored in, or containing fluids or creams	There is an increased risk that leachables can be transferred into the fluid, or cream, and then absorbed through the skin.
Fabricated from in-situ polymerizing materials, absorbable materials, or hydrogels	A risk that polymerization or degradation products can change over time. The manufacturing process can impact the type and quantity of intermediate and final chemicals present in the device, which could introduce a toxicity risk.
Contacts breached or compromised surfaces, such as abraded or shaved skin, or open or healing wounds	An increased risk that leachables can be transferred through breached or compromised skin.
Reprocessed single-use devices	FDA is unaware of the history of safe use of single-use devices that are reused after reprocessing. Reprocessing of such devices can cause adverse biological responses (e.g., irritation).
Includes adhesives to attach a device directly to the skin (e.g., electrode pads, on-body pump attachment systems)	Adhesives can cause adverse biological responses (e.g., irritation).

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What About Metals?

Why are metals like Stainless Steel, Titanium, and Aluminum not on the list?

- Nickel sensitivity?

Does this mean I have to test metal components?

- You can apply to add materials
- It does not exclude you from running a risk assessment on any material and provide a justification

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