Mind the GAP(s)

Practical guide to biocompatibility

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- Background
- Biological Safety Evaluation
  - Risk Based
  - Device categorization
  - Product understanding
  - Challenges
  - Evidence gaps
  - Control measures
- Biological Safety Report
- Chemical characterization
- Summary

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Measure, Monitor & Motivate
Connected health devices

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Biological Safety Evaluation

– Risk based (ISO 10993-1/ISO 14971)

The biological evaluation of any material or medical device intended for use in humans shall form part of a **structured biological evaluation program** within a risk management process in accordance with ISO 14971 [ISO 10993-1].

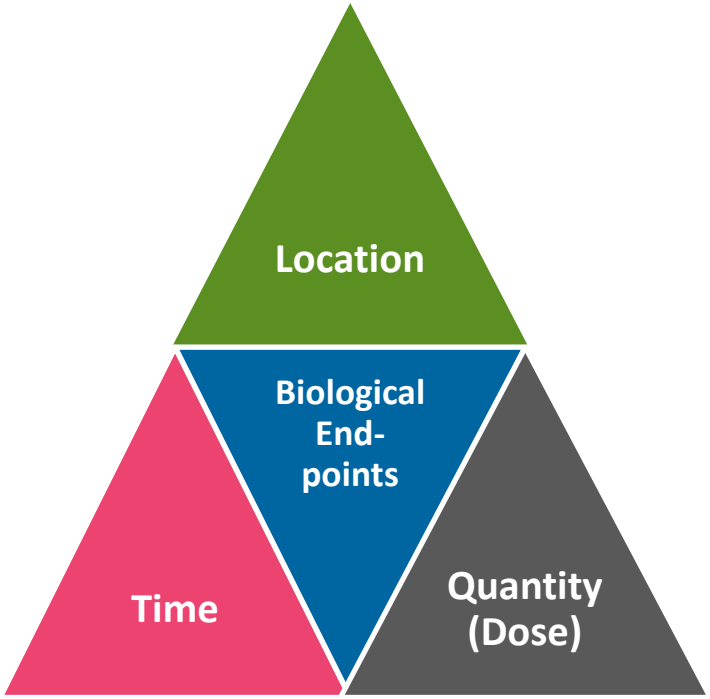
The purpose of testing is to obtain **additional** data which can assist in reaching a conclusion. A **rationale for testing** should therefore be based on an analysis of the relevant risks which are indicated from the existing data. [ISO/TR 15499]

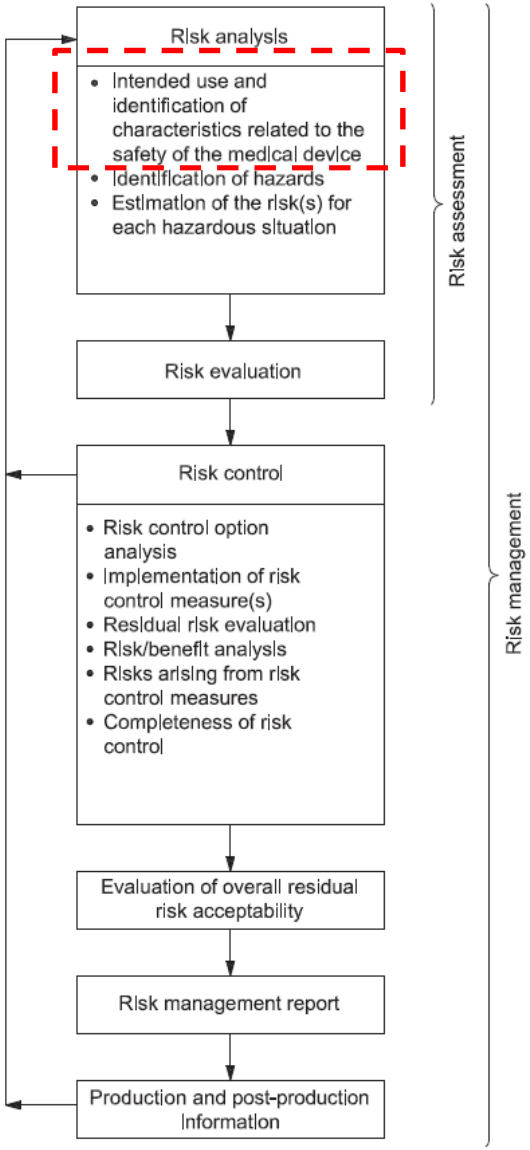
All biological effects included in the matrix may not be relevant for all devices. Thus, the modified matrix is only a framework for the selection of endpoints for consideration and **not a checklist of required biocompatibility testing**. [FDA Guidance 1811]

evaluation ≠ testing

Characteristics of Medical Device

- Use – Exposure to the human body





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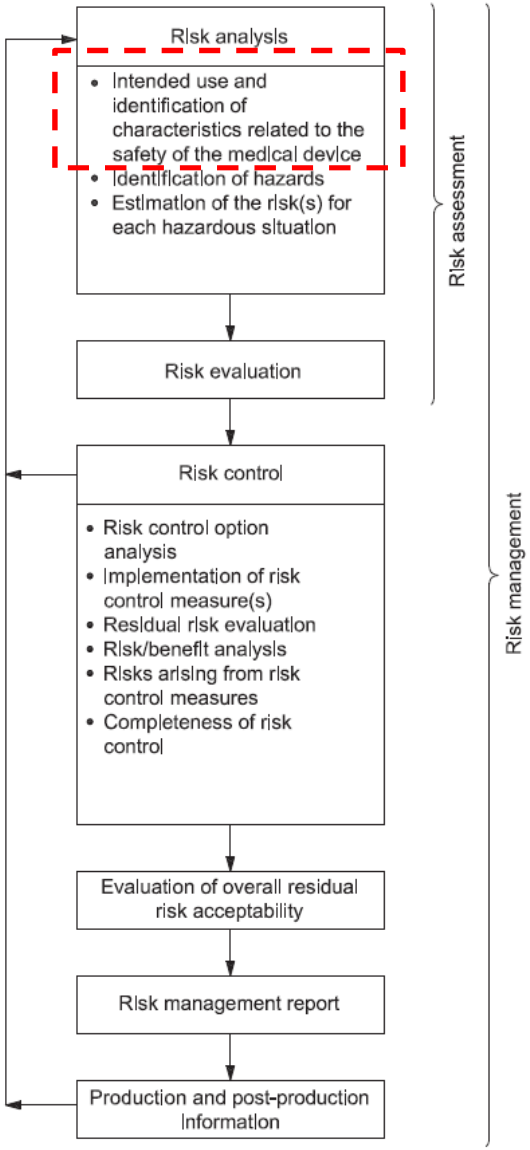
Nature and duration of exposure

Philips health watch and Philips health band:

- Device Category: Surface Contacting
- Contact: Intact Skin
- Duration of exposure: Permanent



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Biocompatibility Evaluation Endpoints

Medical device categorization by			Biological effect													
Nature of Body Contact		Contact Duration	Cytotoxicity	Sensitization	Irritation or Intracutaneous Reactivity	Acute Systemic Toxicity	Material-Mediated Pyrogenicity	Subacute/Subchronic Toxicity	Genotoxicity	Implantation	Hemocompatibility	Chronic Toxicity	Carcinogenicity	Reproductive/Developmental Toxicity#	Degradation@
Category	Contact	A – limited (≤24 h) B – prolonged (>24 h to 30 d) C – permanent (> 30 d)													
Surface device	Intact skin	A	X	X	X										
		B	X	X	X										
		C	X	X	X										
	Mucosal membrane	A	X	X	X										
		B	X	X	X	O	O	O		O					
		C	X	X	X	O	O	X	X	O		O			
	Breached or compromised surface	A	X	X	X	O	O								
		B	X	X	X	O	O	O		O					
		C	X	X	X	O	O	X	X	O		O	O		
External communicating device	Blood path, indirect	A	X	X	X	X	O				X				
		B	X	X	X	X	O	O			X				
		C	X	X	O	X	O	X	X	O	X	O	O		
	Tissue+/bone/dentin	A	X	X	X	O	O								
		B	X	X	X	X	O	X	X	X					
		C	X	X	X	X	O	X	X	X		O	O		
	Circulating blood	A	X	X	X	X	O		O^		X				
		B	X	X	X	X	O	X	X	X	X				
		C	X	X	X	X	O	X	X	X	X	O	O		
Implant device	Tissue+/bone	A	X	X	X	O	O								
		B	X	X	X	X	O	X	X	X					
		C	X	X	X	X	O	X	X	X		O	O		
	Blood	A	X	X	X	X	O		O	X	X				
		B	X	X	X	X	O	X	X	X	X				
		C	X	X	X	X	O	X	X	X	X	O	O		

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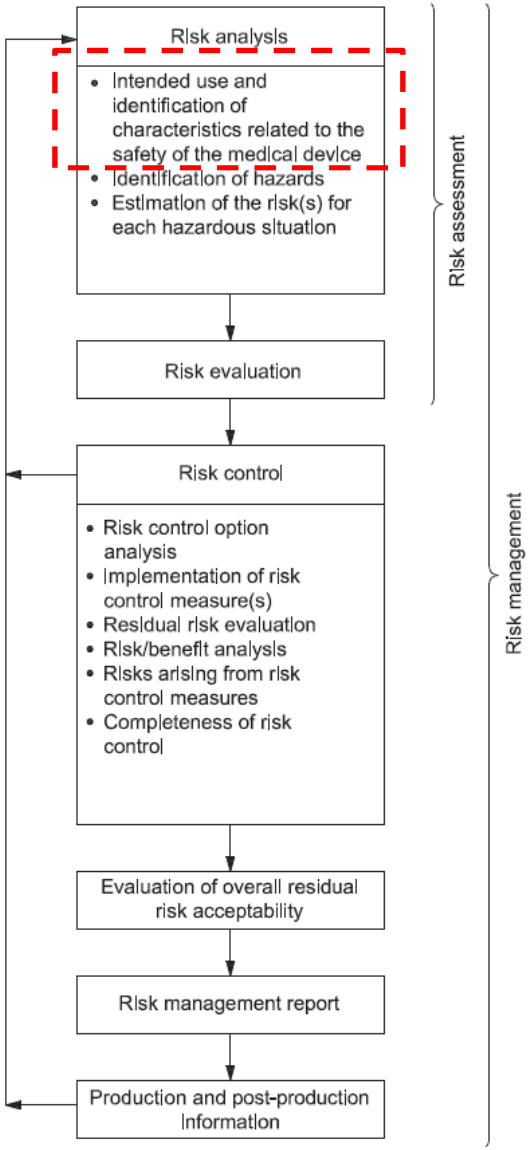
Design characteristics

- Final product / versus development
- Design (composition)
  - composing components
  - additives
  - leachable substances
  - degradation products
  - final chemical and physical characteristics
  - interaction with other products/components (accessories, package materials)



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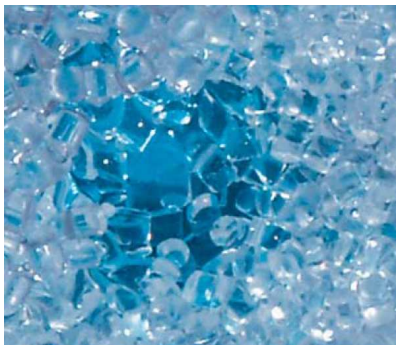
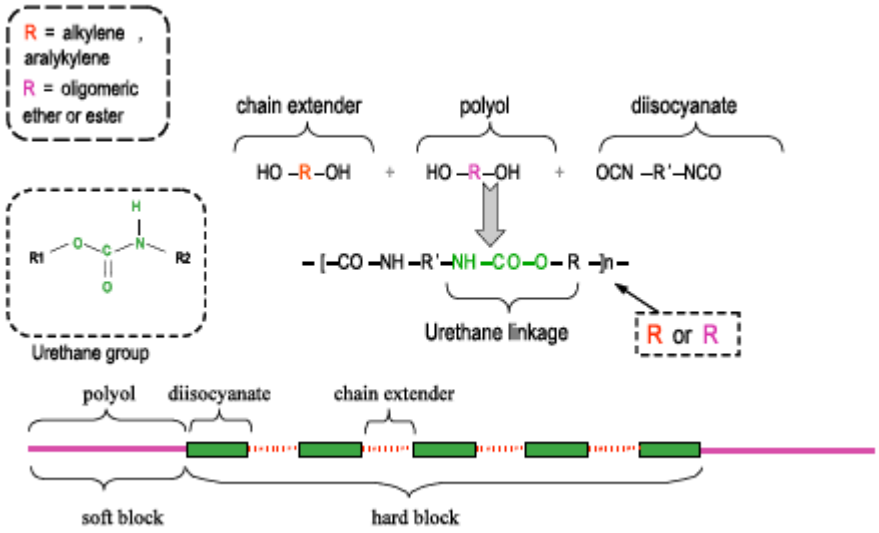
Thermoplastic polyurethane (TPU)

- **Aromatic TPUs** based on isocyanates like MDI are workhorse products and can be used in applications that require flexibility, strength and toughness.





Source: www.Huntsman.com

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Thermoplastic polyurethane (TPU)

8. Exposure Controls/Personal Protection

Exposure Limits

Thermoplastic Polyurethane (TPU) is generally non-hazardous under ambient conditions., The following exposure limits do not apply to the product in its supplied form; however, when the product is heated (i.e, during processing or thermal decomposition conditions), there is a potential for the release of 4,4'-diphenylmethane diisocyanate (MDI) vapors.

4,4'-Diphenylmethane Diisocyanate (MDI) (101-68-8)

US. ACGIH Threshold Limit Values
Time Weighted Average (TWA): 0.005 ppm

US. OSHA Table Z-1 Limits for Air Contaminants (29 CFR 1910.1000)
Ceiling Limit Value: 0.02 ppm, 0.2 mg/m3

Source: www.Huntsman.com

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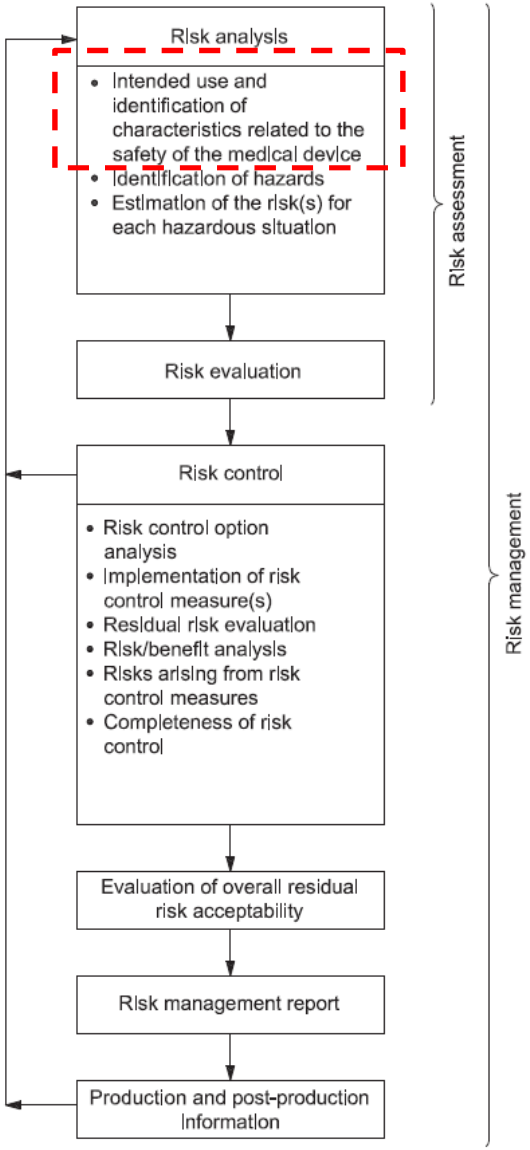
Process characteristics

- purchasing
- manufacturing steps of the various components and final device
- processing agents and cleaning steps
- sterilization process effects
- packaging process
- storage conditions
- aging



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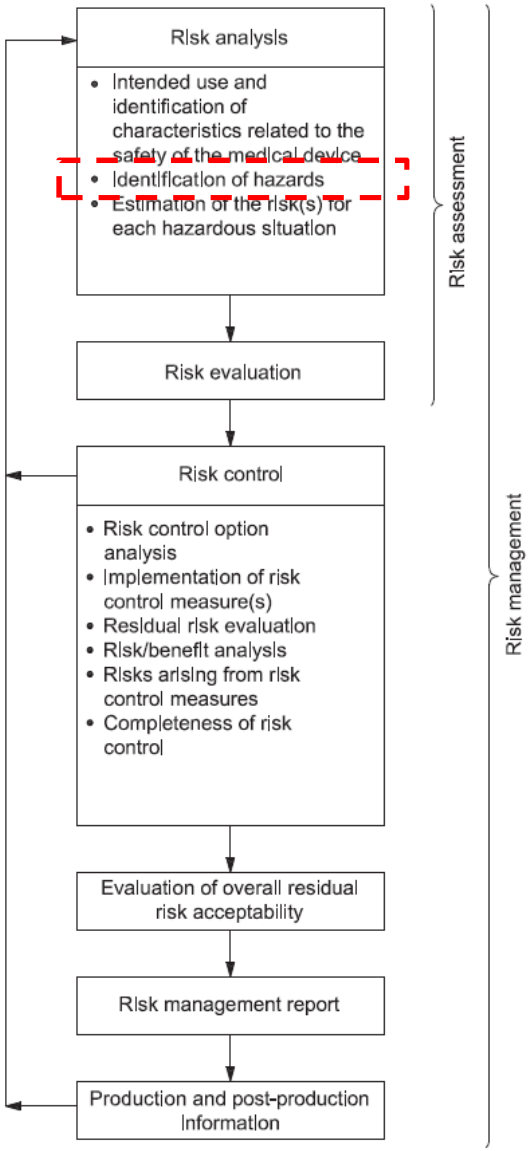
Identification of hazards

- Importance and relevance of:
  - Material data (‘medical grade’)
  - Process data (need to understand material behavior)
  - Manufacturing control (importance of supplier control)
  - Clinical data/Literature/PMS data
- toxicity of each material component?
- Known toxic effects?
- What is the dose-response relationship?



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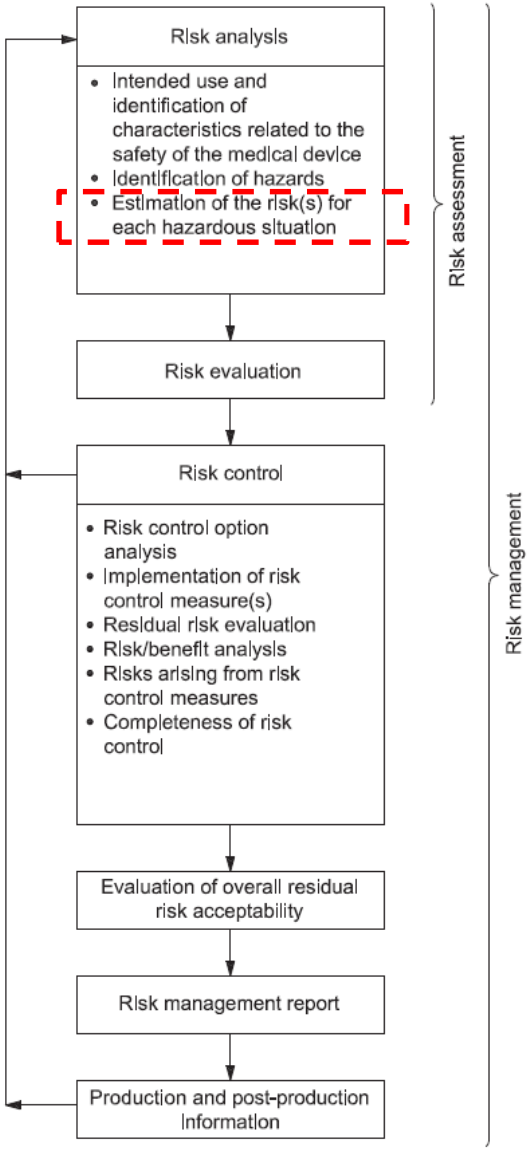
Risk estimation

- What do we know so far?
- Toxicology?
  - Consulting a toxicologist
    - Toxicological databases
    - Routes of administration
    - No Observed Adverse Effect Level (NOAEL), Low Observed Adverse Effect Level (LOAEL), Derived No Effect Level (DNEL), Etc.



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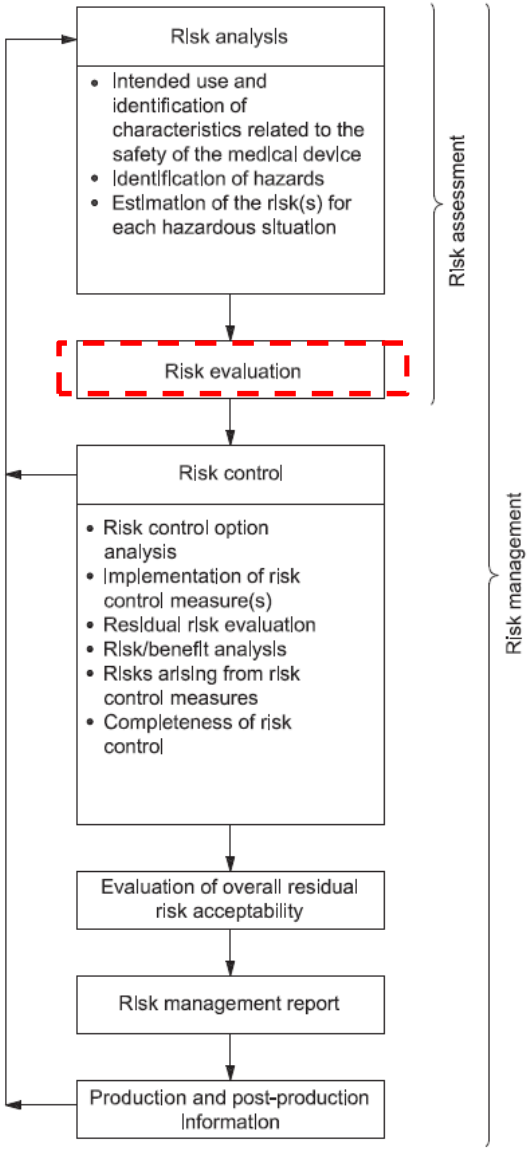
Risk evaluation

– What are the gaps?

- Testing required?
  – In Vivo versus In Vitro
- Acceptability criteria?
- GLP (ISO 17025/FDA 21CFR 58)



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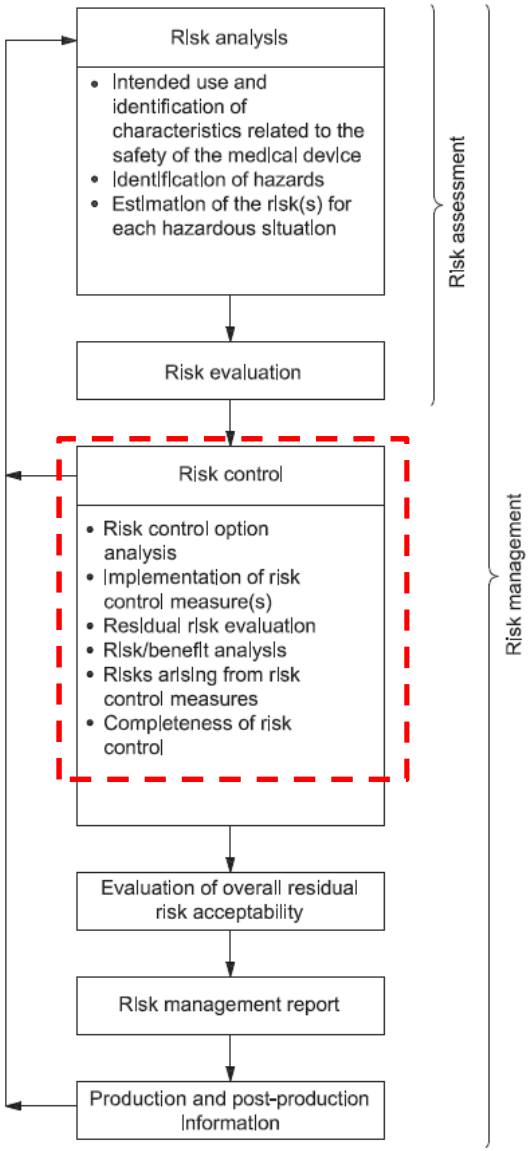
Risk control

- Did we meet the acceptance criteria?
- Options:
  - Change design
  - Change material/additives
  - Manufacturing controls
  - Provide warning



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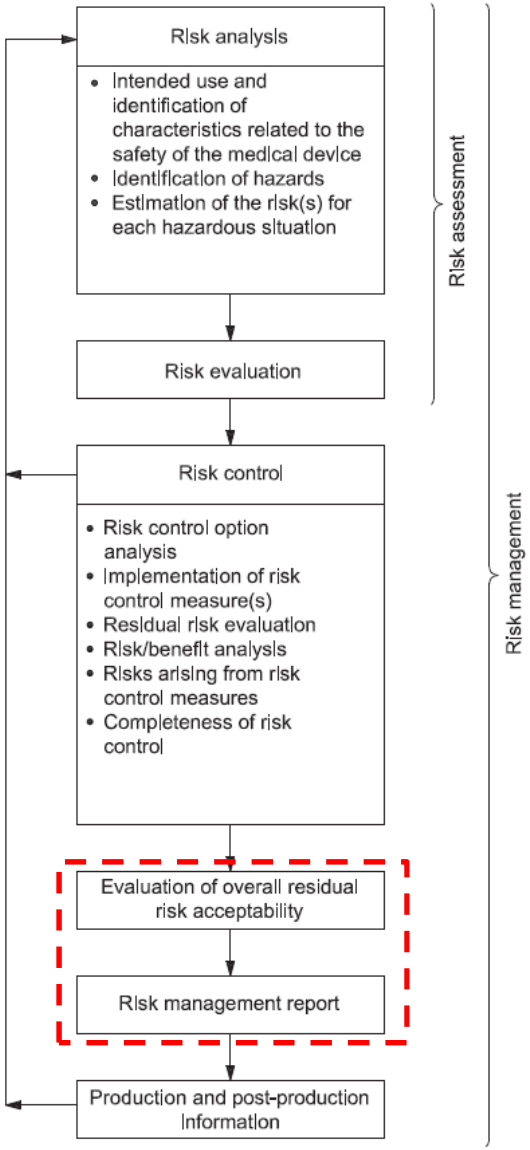
Biological Safety Report

– Complete evaluation and create biological safety report

- Incorporate test results,
- Report residual risk,
- Draw final conclusions about acceptability of device.



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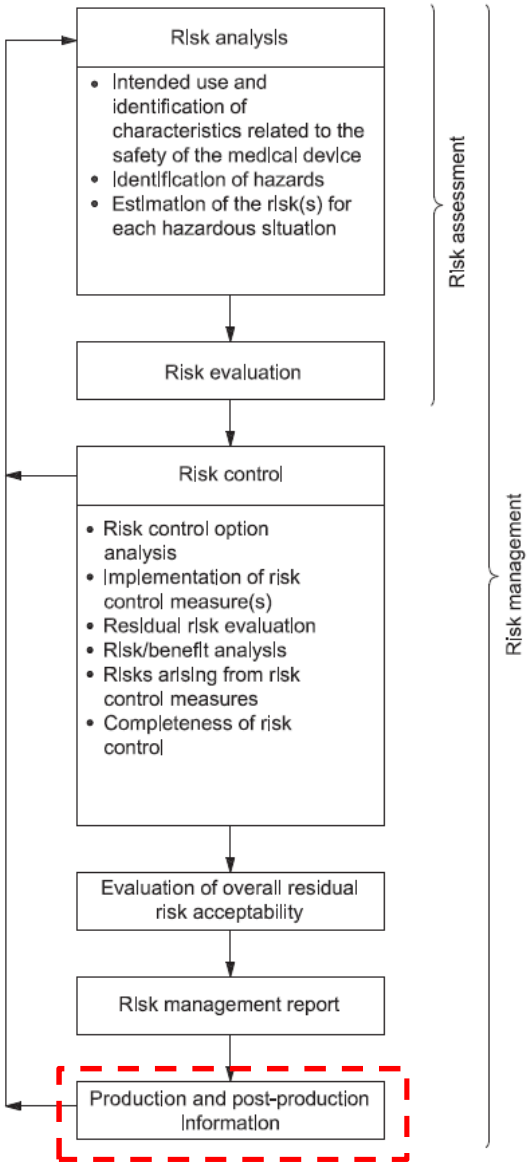
Production and PMS data

- Risk assessment are living documents
  - Monitor device in clinical use (trend analysis, adverse events)
  - Update risk assessment (Post-market surveillance data, supplier/design/material changes)



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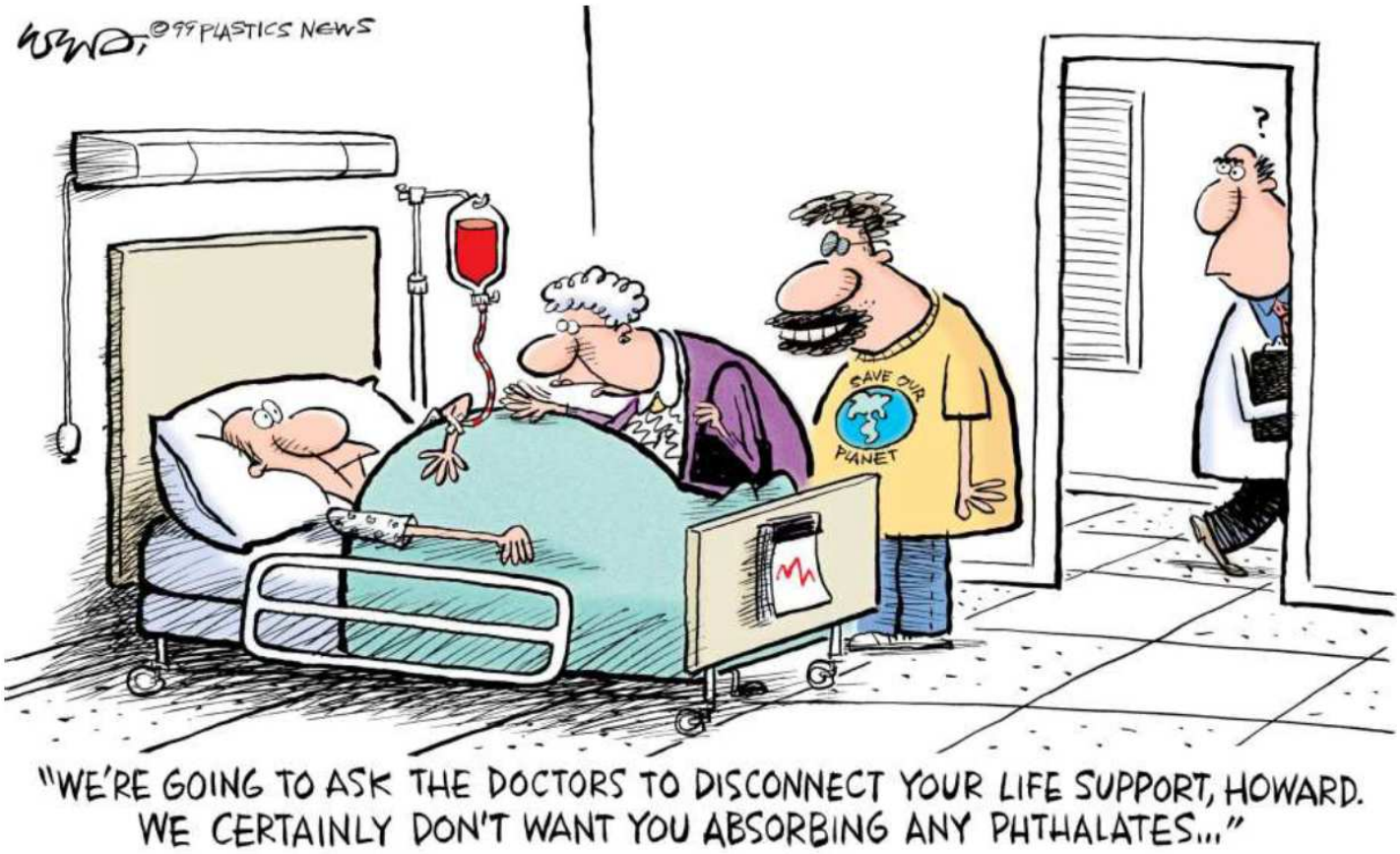
Increasing importance chemical characterization

- Material/Process Changes,
  - Creating a baseline for:
    - Change material supplier,
    - Change in manufacturing process
    - Introducing new features (e.g. new colors)
- Supplementing in vivo Biocompatibility testing
  - Animal testing policy
  - Substantiate the need for limited testing
- Regulatory reviewer request

Summary

- Don’t underestimate the complexity or the impact biocompatibility has on the success rate of putting safe products on the market.
- Make sure the right people are on board and that they understand the intended use of your device.
- The right knowledge/experience is essential in avoiding the potential gap(s).
- Make sure when you start a project you already take biocompatibility into account.
- Be prepared for the future. Making the right choices or design decisions at the start can prevent the need for unwanted testing in the future.

Questions?



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