Biological safety evaluation of medical devices: A risk management process

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Treatment BEFORE CE

Treatment AFTER CE

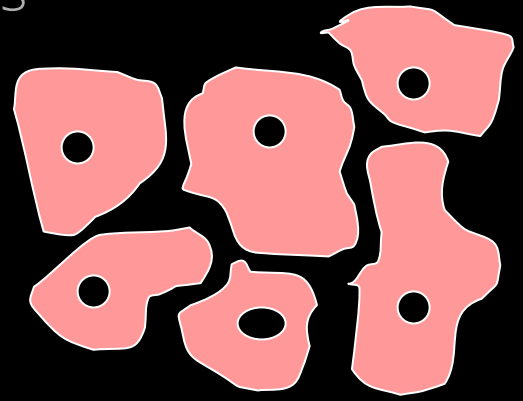
Design process

Biocompatible?

surface structure
chemical surface characteristics
degradation products / wear products
leachable substances

material

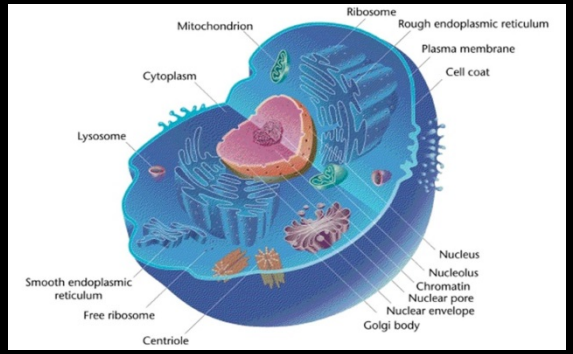
enzymes
antibodies
proteins
phagocytosis

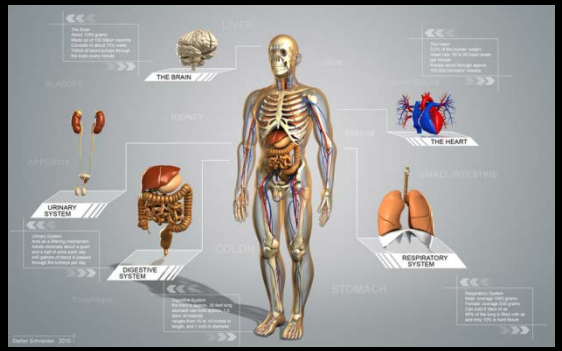


tissue
cells

Biocompatible

Evaluate
at
different levels !





Biocompatible

Stent → no blood clotting

Haemostat → blood clotting

Biocompatible

Non degradable suture → no inflammatory response

Degradable suture → inflammatory response

Biocompatible

Material performs
satisfactory
in the intended application

MDD/MDR (Annex I: Req. 1)

Devices shall be designed and manufactured in such a way that they are safe to patient / user

when used under conditions and purposes intended

MDD/MDR (Annex I: Req. 2/ 2-4)

Design conform safety principles:

- Acceptable risks when weighted against benefits
- Elimination
- Reduction of risks
- Residual risks: - protection measures
  - information (IFU)

MDD/MDR (Annex I: Req. 7/10)

Points of attention:

- Choice of materials
- Contaminants / residues: e.g. from production
- Compatibility: medicinal substances, package material
- Compatibility materials ↔ tissues, cells, body fluids (ADME)
- Tissue exposure: type, duration, frequency

MDR (Annex I: Req. 10)

Special attention:

- Mechanical, physical and chemical characteristics
- Debris, particles, degradation products, leachables, nanomaterials (1 nm to 100 nm)

MDD/MDR (Annex 1: Req 7.5/)

Special attention:

- Devices
  - intended to administer medicines, body liquids, substances to or from the body
  - intended for transport/storage such body fluids, substances
  - Invasive or come into direct contact

- Devices containing substances at **>0.1% w/w** and which are
  - **carcinogenic, mutagenic** or **toxic to reproduction** (CMR)
    (EC 1272/2008 Annex VI part 1- category 1A and 1B)
  - **endocrine-disrupting** properties
    (EC 1907/2006 Art.59 REACH, EC 528/2012 Art5(3) biocidals)

- Justification + info residual risks (IFU) for use
  - treatment children/ pregnant/ nursing women/ vulnerable patient groups

How?

EN ISO 14971:

Application of risk management to medical devices

EN ISO 10993:

Biological evaluation of medical devices

Part: 1 – 20+

EN ISO 10993 series

Part:

1. Evaluation and testing within a risk management process (REV)
2. Animal welfare requirements
3. Tests for genotoxicity, carcinogenicity, reproductive toxicity
4. Selection of tests for interaction with blood
5. Tests for cytotoxicity: in vitro methods
6. Tests for local effects after implantation
7. Ethylene oxide sterilization residuals

EN ISO 10993 series

Part:

8. *(withdrawn see 12)*
9. Framework for the identification and quantification of potential degradation products
10. Tests for irritation and sensitization
11. Tests for systemic toxicity
12. Sample preparation and reference materials
13. Identification and quantification of degradation products from polymeric medical devices
14. .... from metals and alloys
15. .... from ceramics

EN ISO 10993 series

Part:

16. Toxicokinetic study design for degradation products and leachables
17. Methods for the establishment of allowable limits for leachable substances
18. Chemical characterization of materials
19. Physico-chemical, mechanical and morphological characterization (TS)
20. Principles and methods for immunotoxicological testing of medical devices (TS)
22. Guidance on nanomaterials (TR)
33. Supplement to ISO 10993-3 — Guidance on tests to evaluate genotoxicity (TR)

EN ISO 10993 series

- ISO/TR 15499 Guidance on conducting a biological evaluation
- ISO 30993 Terminology
- ISO/PDTR 29741 Development of tolerable intake values for Di(2-ethylhexyl)phthalate (DEHP)
- ISO/PDTR Principles and methods for pyrogen testing of medical devices
- ISO/DTR 37137-1 Absorbable implants
- ISO/DTR 37137-2 Absorbable metals

Only Europe?

Some countries have their own specific requirements!

Design characteristics

Subjects	Characteristics
Indication	Disease, condition, adult, child
Mode of action/ functionality	pH, osmolarity, strength, degradation, 3D, coating smooth/ porous/ matrix/ liquid/ gel/ cream
Application/exposure	Tissue type/ contact duration/ frequency
Composition	polymer, metal, ceramic …
Production/sterilization	Moulding, cleaning / EtO, Gamma, dry-moist heat
Store/transport	Package system
Stable during shelf life	3 years
Stable during use	3 months, 15 years
Use in combination	Accessories, devices, drug

ISO 10993-1:Exposure

Nature of body contact		Example
Category	Contact	
Surface device	Skin	electrodes, ext. prostheses
	Mucosal membrane	contact lenses, urinary catheters, dental prostheses
	Breached surfaces	wound dressings
External communicating device	Blood path, indirect	blood administration sets
	Tissue/bone/dentine	draining systems, dental filling, laparoscope
	Circulating blood	intravascular catheters, dialysis systems, electrodes
Implant	Tissue/bone	orthopaedic implants, pacemaker, breast implants
	Blood	heart valves, stents, vascular prostheses

ISO 10993-1:Exposure

Exposure	Duration: Single use / sum repeated contact
No	-
Transient	< min
Limited	< 24 hours
Prolonged	24 hours – 30 days
Permanent	> 30 days

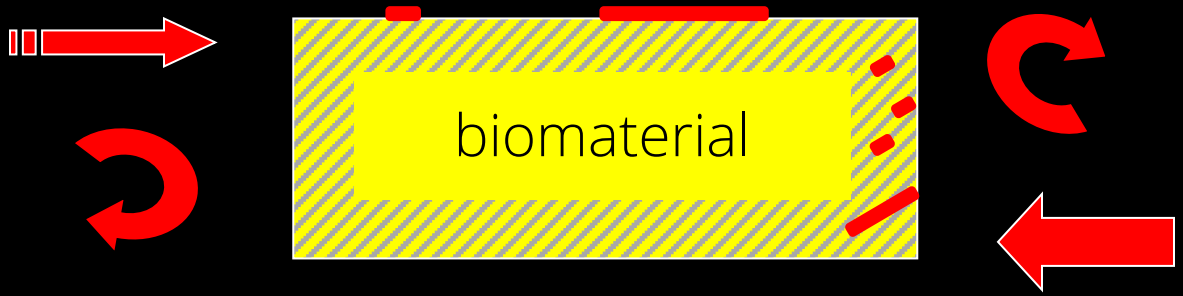
Medical device categorization by			Endpoints of biological evaluation													
Nature of Body Contact		Contact Duration	Physical and/or chemical information	Cytotoxicity	Sensitization	Irritation or intracutaneous reactivity	Material mediated pyrogenicity [a]	Acute systemic toxicity	Subacute toxicity	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		

Chemical / Physical

- Chemical characterization components (part 18)
- Additives, anti-oxidants, color agents, residues (part 18)
- Degradation products (part 9, 13, 14, 15)
- Physico-chemical, mechanical, morphological (part 19)

  +/- surface, moving parts, porosity, surface roughness, sharp/thin fibers, microspheres, liquid/gel, 3D matrix
- Nanomaterials (part 22)
- Process residues (part 12, 18)

Know the production process!

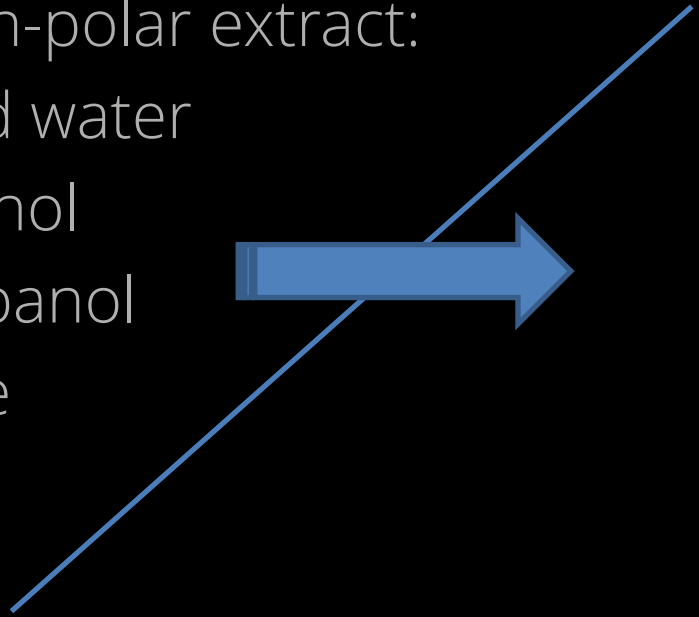


Components used during productioncan influence the biocompatibility of the device!

Extract & analysis (part 12)

Polar / Non-polar extract:

- Purified water
- % Ethanol
- Isopropanol
- Hexane



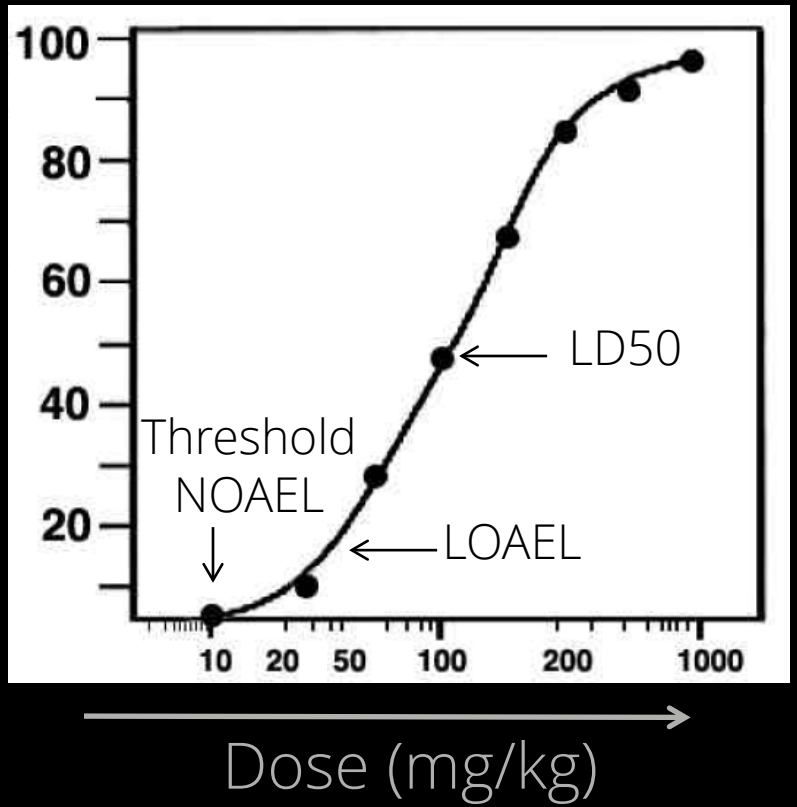
Analytical method:

- GC/MS
- HPLC/MS
- HPLC/GCP
- IPC
- FTIR

Extract & analysis (part 12)

Qualify		Quantify
Acetone	CAS No. 67-64-1	XX µg/device
di-(2-ethylhexyl) phthalate (DEHP)	CAS No. 117-81-7	XX µg/device

Part 17: Allowable limits



Uncertainty Factors

Know the composing material!

Review toxicology and other biological safety data:

- Components/material
- Information on prior use:
  - in “own” products (same use?)
  - in “other” products (same materials?)
- Potential leachables

Info source:

- Suppier: MSDS, tests
- Sci. Literature (e.g. PubMed): equivalency?
- Database; TOXLINE, TOXNET, EPA IRIS, EPA, ATSDR, Reports from Authorities, USP, ICH, OECD SIDS, WHO

Biological evaluation

Hazard	Literature	Testing	Rational
Cytotoxicity		X	
Irritation	X	X	
Sensitization		X	
Acute systemic toxicity	X	X	
Subchronic/chronic systemic toxicity	X	X	
Local tolerance		X	
Genotoxicity	X	X	
Reproductive toxicity	X		X
Carcinogenicity	X		X

Testing

- Select appropriate laboratory (GLP)
- Validated test models
- Final product/ representative sample
- Test set-up reflects performance/application
- Controls and reference materials
- Extract (polar/non-polar, temperature, time)

Testing: Extraction ratio (part 12)

Table 1 — Standard surface areas and extract liquid volumes

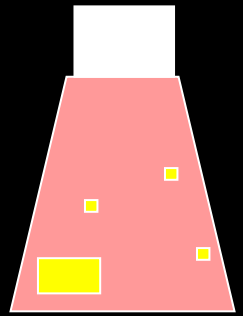
Thickness mm	Extraction ratio (surface area or mass/volume) ± 10 %	Examples of forms of materials
< 0,5	6 cm^2/ml	film, sheet, tubing wall
0,5 to 1,0	3 cm^2/ml	tubing wall, slab, small moulded items
> 1,0	3 cm^2/ml	larger moulded items
> 1,0	1,25 cm^2/ml	elastomeric closures
Irregularly shaped solid devices	0,2 g sample/ml	powder, pellets, foam, non-absorbent moulded items
Irregularly shaped porous devices (low density materials)	0,1 g/ml	membranes

NOTE While there are no standardized methods available at present for testing absorbents and hydrocolloids, a suggested protocol is as follows:

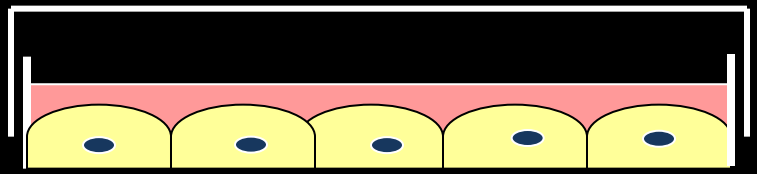
— determine the volume of extraction vehicle that each 0,1 g or 1,0 cm^2 of material absorbs;
— then, in performing the material extraction, add this additional volume to each 0,1 g or 1,0 cm^2 in an extraction mixture.

Part 5: Cytotoxicity

First screening!
In vitro ⟷ in vivo?



culture medium
weight-surface/volume
37°C – 24h



<u>24-72h:</u>
morphology
proliferation
metabolism
} scoring

Part 10: Irritation

Extract:

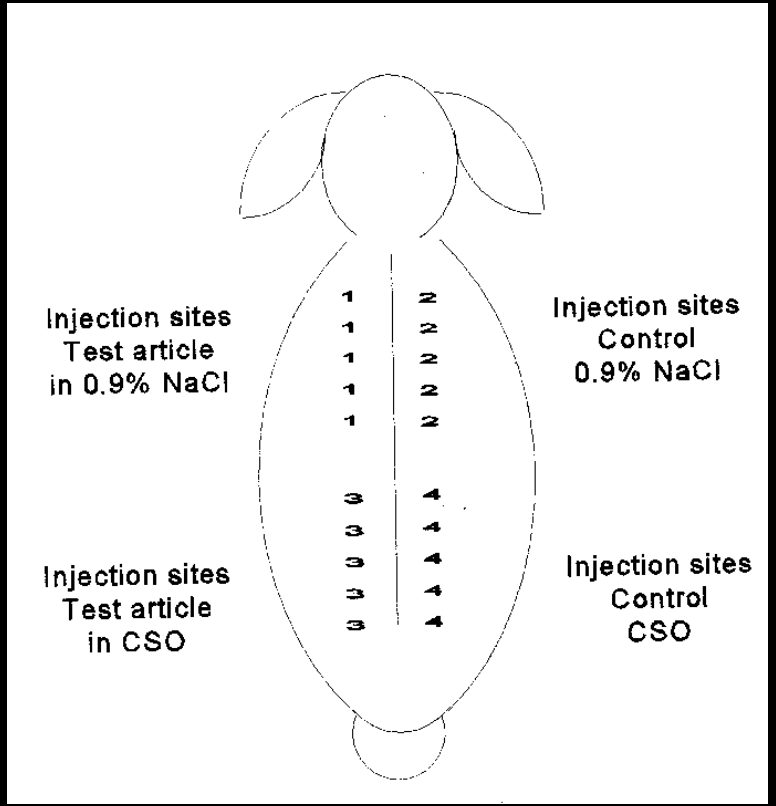
NaCl, Cotton Seed Oil - 37°C, 72h

Rabbit (3):

- IC injection

Scoring: 24, 48, 72h after injection

- Erythema (redness)
- Edema



Part 10: Sensitization (allergy)

Extract:

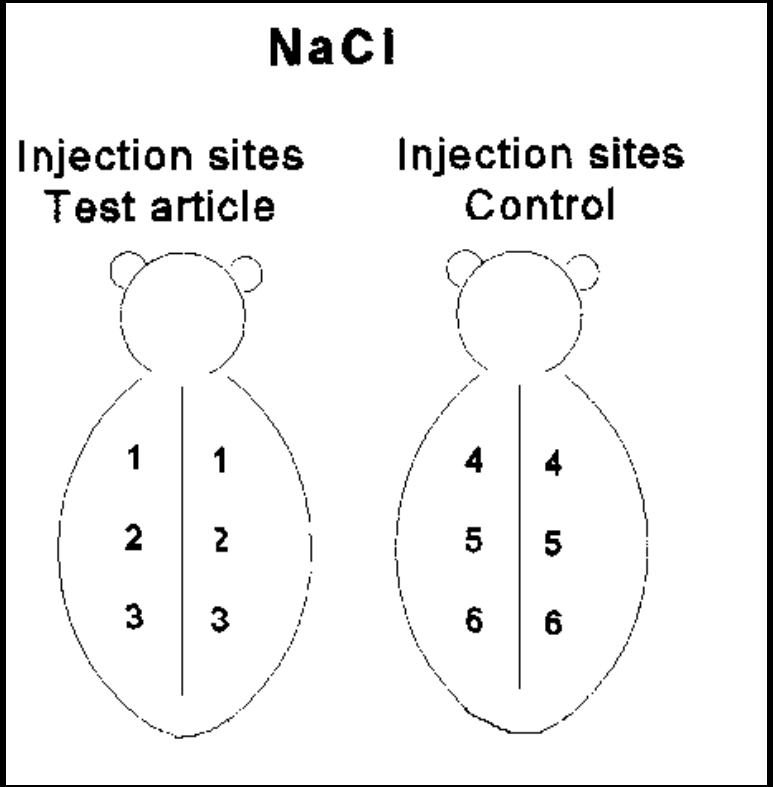
NaCl, Cotton Seed Oil - 37°C, 72h

Guinea pigs (10):

- Induction phase: ID inj + skin (1 week)
- Rest phase: 2 weeks
- Challenge phase: skin

Scoring: 24, 48, 72h after application

- Erythema
- Edema



Part 11: Systemic toxicity (acute)

Extract:

NaCl, Cotton Seed Oil - 37°C, 72h

Mouse (10):

- Injection I.V., I.P. – X times

Scoring: 4, 24, 48, 72h after injection

- Behavior, breathing, irritation, eyes, diarrhea, weight, tremors, death

Part 11: Systemic toxicity

- Sub acute: up to 4 weeks
- Sub chronic: up to 13 weeks
- Chronic: >4-6 months - 1 year
- Carcinogenicity: lifetime

Rodents (SC, IV, IM):

- gross morphology, weight organs
- histopathology organs, tissues
- blood sampling: - hematology (e.g. blood cells, mponents)
  - biochemistry (e.g. enzymes)

Part 6: Local tissue reaction

- Animal model
- Observation times
- Tissue: subcutane, intramuscular, bone

Test material – Control material:

- Solid, powder, paste
- Surface characteristics
- Degradable

Surgical technique!!!

Part 6: Local tissue reaction

Macroscopical:

- surrounding tissue, color, vascularisation

Microscopical:

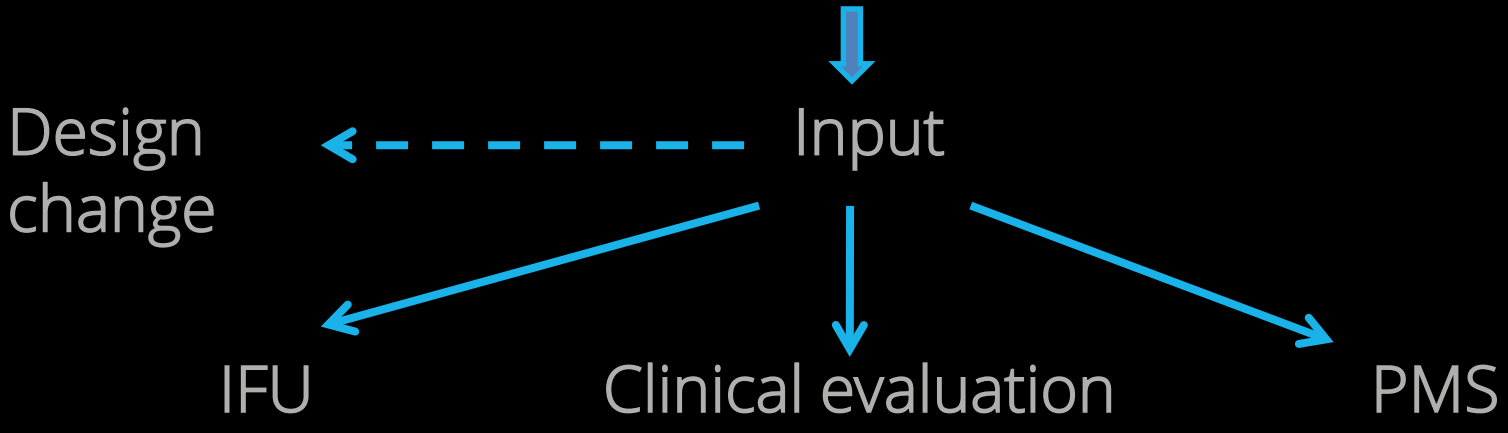
- fibrous capsule, fibrosis, granuloma
- changes in tissue morphology
- inflammatory cells: macrophages, giant cells, polymorphnuclear leucocytes (eosinophils, basophils, neutrophils), lymphocytes
- necrosis, cell debris
- fatty tissue
- quality, quantity of tissue ingrowth

Report

- Introduction/scope/objective
- Description product
- Description process
- Potential hazards/ harm
- Chemical characterization (leachables, tox data, MoS)
- Summary test results
- Rationals
- Overall conclusion
- References

Link to other processes

Overall conclusion: are risks acceptable?



Re-evaluation

- Change in:
  - Source/ material specifications/design
  - Package system
  - Production process, sterilization
  - Intended use
- Adverse effects:
  - Complaints
  - PMS

Thank you for your attention!

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