
Good Manufacturing Practices
ATLAS Project - NTA1

Short presentation

What is this course about ?

- Good Manufacturing Practices
  - Set of rules and good practices for manufacturing medical devices, per FDA/CE guidelines

- Specific aspects for design of robots
  - Biocompatibility
  - Sterilization
  - Links with design and material choices

What is this course NOT about ?

- Disclaimer: I'm not an expert about the MDD or FDA rules
  - This course does not provide legal advice about how to put a device to the market, or how to manufacture it accordingly

- Rather, I'll give feedback coming from previous experiences with designing devices for (pre)clinical use

Part I – Materials

Notion of biocompatibility

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Leading opinion

There is no such thing as a biocompatible material

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ABSTRACT

This Leading Opinion Paper discusses a very important matter concerning the use of a single word in biomaterials science. This might be considered as being solely concerned with semantics, but it has implications for the scientific rationale for biomaterials selection and the understanding of their performance. That word is the adjective 'biocompatible', which is often used to characterize a material property. It is argued here that biocompatibility is a perfectly acceptable term, but that it subsumes a variety of mechanisms of interaction between biomaterials and tissues or tissue components and can only be considered in the context of the characteristics of both the material and the biological host within which it placed. *De facto* it is a property of a system and not of a material. It follows that there can be no such thing as a biocompatible material. It is further argued that in those situations where it is considered important, or necessary, to use a descriptor of biocompatibility, as in a scientific paper, a regulatory submission or in a legal argument, the phrase 'intrinsically biocompatible system' would be the most appropriate. The rationale for this linguistic restraint is that far too often it has been assumed that some materials are 'universally biocompatible' on the basis of acceptable clinical performance in one situation, only for entirely unacceptable performance to ensue in quite different clinical circumstances.

- "There is no such thing as a biocompatible material"
  - Notion of system
  - Interaction with the body
  - Realization of a function

Interaction with the body

- Carcinogenicity : does the material induce cancer ?
- Immunogenicity : does it induce a immune reaction in the body ?
- Teratogenicity : can it cause birth defects ?
- Toxicity : is the material causing toxic of inflammatory response ?
- Mechanical resistance and resistance to corrosion
- Importance of the time factor: is the device in contact with tissues in a short-term fashion (e.g. single use device) or long-term (e.g. implantable device) ?

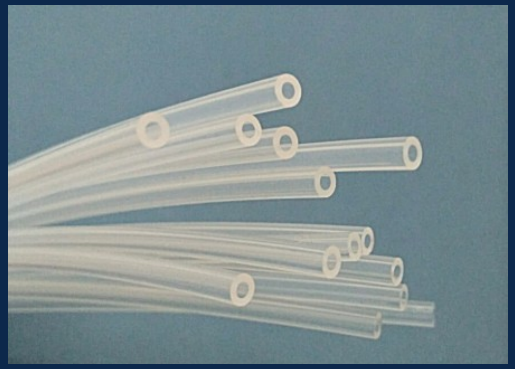
A case study : PTFE

- PolyTetraFluoroEthylene, often known as Teflon

- Basic properties
  - Very hydrophobic
  - Chemically inert
  - Very low friction coefficient (3rd lowest of all known materials)

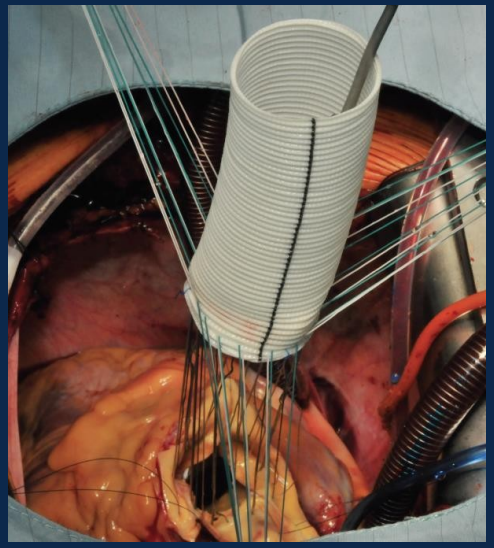
- Used in a lot of applications

PTFE in medical devices



Tubing

Non-stick coating on various devices



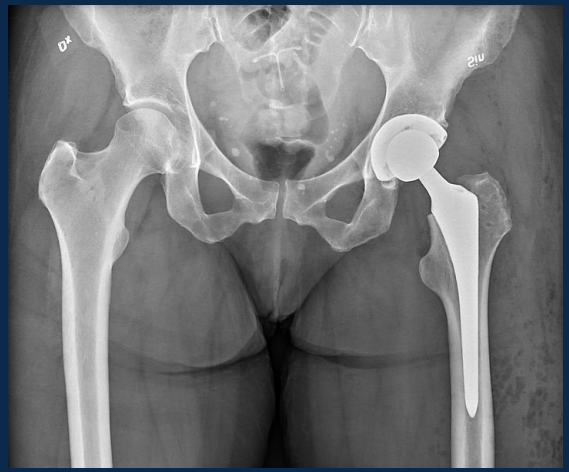
Vascular grafts

Typical example of a “biocompatible material” ?

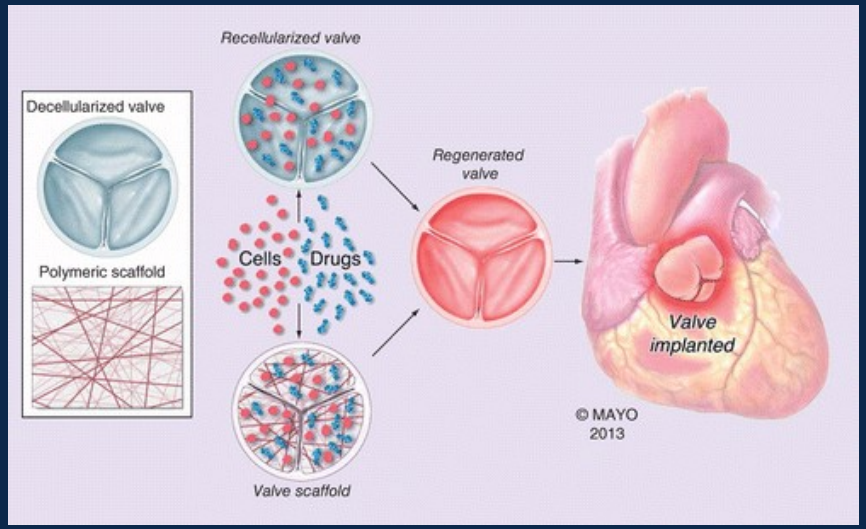
PTFE in hip prosthesis

- PTFE in the acetabular cup ?
  - Low friction
  - High durability
  - Chemically inert
  - Hydrophobic

- Used in the first prosthesis designs (1964)
  - Repeated friction causes wear
  - Small particulates/debris amass
  - Massive local inflammatory response !



PTFE in tissue engineering scaffolds



- Aim: growing tissues on a scaffold to produce functional implants
- Scaffold: porous, polymeric material to support cellular growth
- PTFE is hydrophobic
  - Cells will not stick to it
  - Difficult to promote cellular growth

Biocompatiblity is doing no harm to the body, but also make sure that the function can be carried out !

Another case study : Silicone

Due to its inherent purity, inertness and biocompatibility, silicone is an extremely versatile material that lends itself to a broad range of application conditions and is a preferred choice of elastomer in the biomedical, pharmaceutical and healthcare industries. As a liquid raw material, silicone offers advantages in processing that render it a premier choice of material for technical components in high volumes.

Benefits of Silicone

- Consistent mechanical properties from -45 °C to + 180 °C / -49 °F to +356 °F
- Hardness from 10 to 80 Shore A
- Platinum curing gives the highest purity material
- Broad operating temperatures from -50 °C to +250 °C / -58 °F to +482 °F

Extract from a medical grade Silicone manufacturer

Another case study : Silicone

Breast implants

- The PIP scandal
  - PIP: manufacturer of breast implants, selling worldwide
  - 2001: started manufacturing their own silicone in-house instead of buying medical-grade silicone
  - 2009: concerns with high level of implant rupture, causing inflammation and irritation
  - 2013 : Jean-Claude Mas, CEO of PIP, is sentenced to 4 years in prison, 75 k€ of fine, and is banned for life from working in medical services or running a company

PIP scandal : what went wrong ?

Breast implants

- 1) Slight change of the Silicone formula → It's still Silicone, but not biocompatible anymore for the application !
- 2) Change in the manufacturing process without documenting / requesting new approval from the regulatory bodies
  - Assumed it would be accepted ?
  - Breach of good manufacturing practices !
  - Basis for the prison sentence

Part II – Sterilization

What is sterilization ?

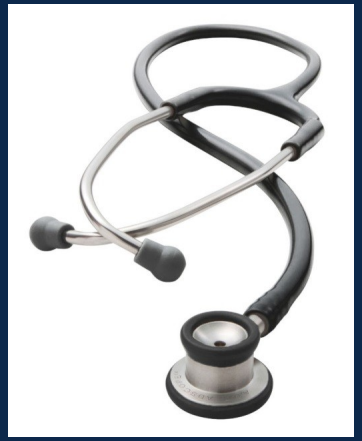
- Sterilization is the process of removing germs and other microorganisms (bacteria, viruses, prions) in a specific surface, object, or fluid

- In the context of medical device development, one must take into account the type of device in order to determine whether sterilization is needed

Medical device categories

- Non-critical devices: contact with skin but not mucous membranes

- Cleaning only necessary
  - Mechanical process : Rising, Rubbing, Water jets, Ultrasound
  - Parameters
    - Time
    - Temperature (<40°C, <65°C)
    - Cleaning solution (concentration, type)

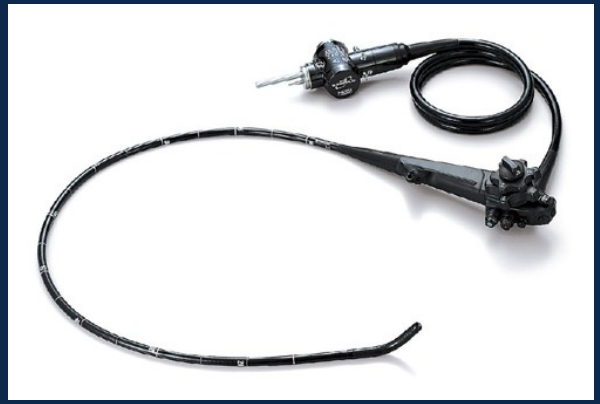


Medical device categories

- Semi-critical devices: contact with mucous membranes or non-intact skin

- Cleaning + disinfection
  - Automated
    - Machine cleaning
    - Thermal disinfection (95°C, 3-5 min, water)

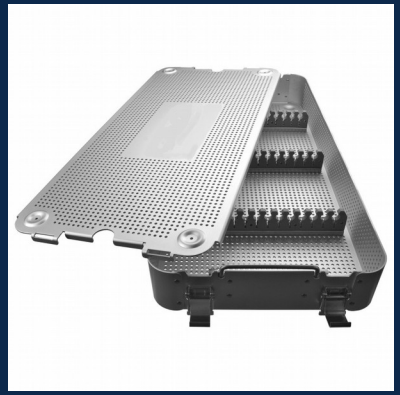
  - Manual (for non-machine cleanable and heat sensitive equipment)
    - Manual cleaning
    - Chemical disinfection (concentration, type)

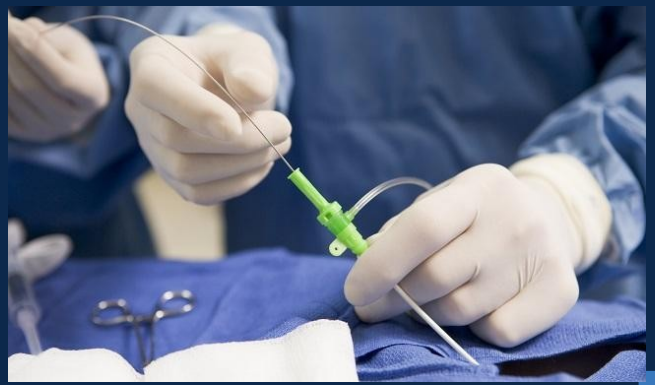


Medical device categories

- Critical devices: contact with vascular system or sterile tissues

- Cleaning + disinfection + sterilization
  - Cleaning
  - Disinfection
  - Control
  - Packing
  - Sterilization





Steam sterilization, a.k.a. autoclave

- Principle: kill microorganisms with moist + heat

- Process:
  - Vacuum, heat the load, and inject steam
  - Keep at 121°C/100 kPa for 15 min **OR** 134°C/200 kPa for 5 min
  - Dry

- Fast
- Efficient
- Simple
- Cheap

- High temperatures
- Moist

Ethylene Oxide, a.k.a ETO sterilization

- Principle: aggressive gas that kills all living elements

- Process:
  - Preconditioning and humidification
  - Inject ETO and expose for ~2-3 hours
  - Evacuation gas
  - Aerate the sterilized device in another room

- Low temperature
- Low humidity
- Wide range of material compatibility

- ETO residues are toxic/carcinogenic if not handled properly
- Long aeration time required (can be days for some porous materials)

Plasma setrilization, a.k.a STERRAD

- Principle: a low-temperature plasma of hydrogen peroxyde attacks the DNA and cell membranes

- Process:
  - Precondition (dry items, packaged)
  - Deep vacuum (50 Pa) and 45°C
  - H202 injection and creation of plasma
  - Vent

- Low temperature
- Many materials
- Non-toxic
- Short cycle and no aeration time required

- Requires specific packaging
- Small sterilization chamber
- No liquids,powders, …
- Problem with lumens !
- Expensive

Other processes

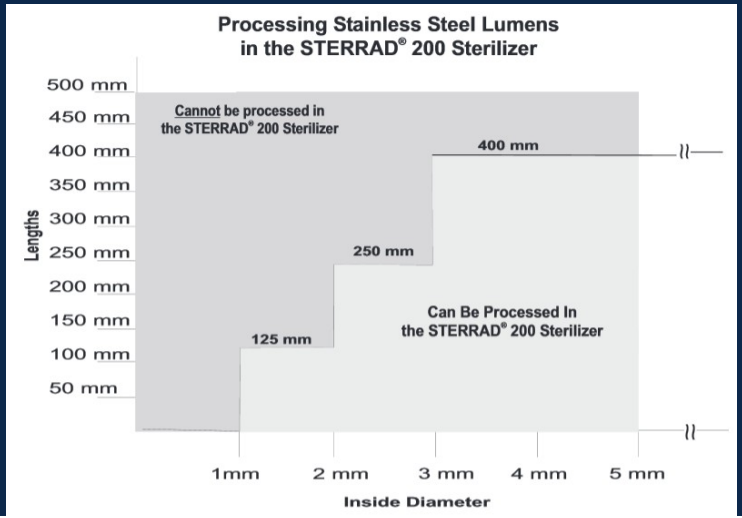
- Ozone
- Gamma/beta radiation
- Glutaraldehyde/Formaldehyde
- Peracetic acid

What happens after sterilization ?

- Sterilizable does **NOT** mean sterile after the process !
  - Reduction of microorganisms by a factor 10^{12}
  - Cleaning & Disinfection → until 10^{6}

Design for sterilization

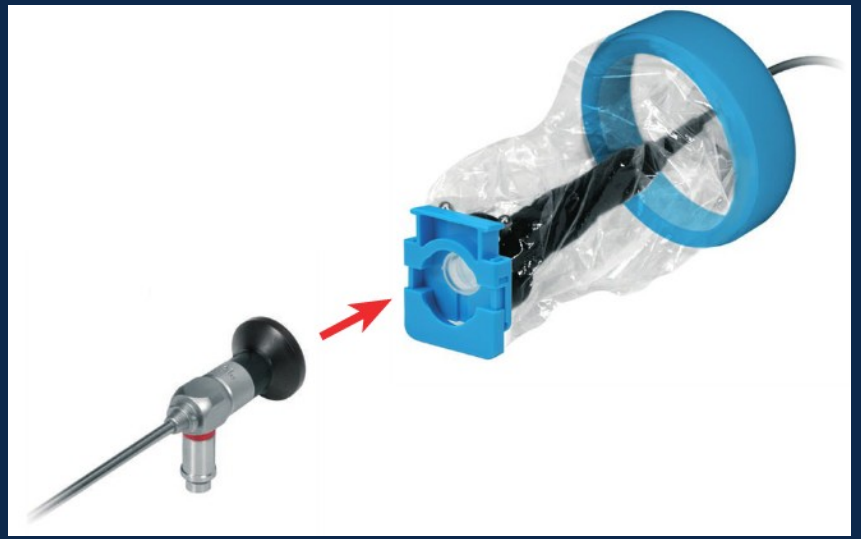
- Lumens in endoscopes: long, narrow channels in critical devices
  - Cleaning with specific bruses
  - Chemical disinfection
  - Sterilization ?



- Steam sterilization: not always possible, sensitive materials
- Plasma setrilization
  - No dead-end lumens
  - Material dependent

Interfaces

- Not everything in a system needs to be sterilized ! Adding setrile interfaces allow for more versatility



Interfaces

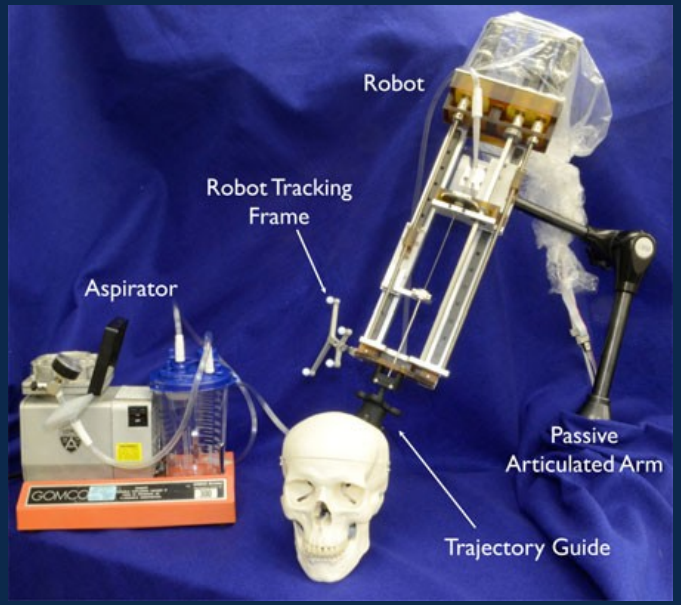


Fig. 3. Sterile barrier concept. (a) Motor plate is removed from the robot before sterilization. (b) Sterile bag is attached to the sterile robot using an aluminum clamp, enabling the motor plate to be subsequently attached and the motors to engage with the Oldham couplings (see Fig. 4). (c) Motor plate is reattached and the bag pulled over it. The robot is now sterile.

Burnger-Kahrs et al, TBME 2013

Conclusion

- Biocompatibility and sterilizability have a huge impact on material and mechanical design choices
- Yet, those complex notions are often overlooked or misunderstood
- Take home messages:
  - Don’t take your own ideas for granted
  - Document your choices !