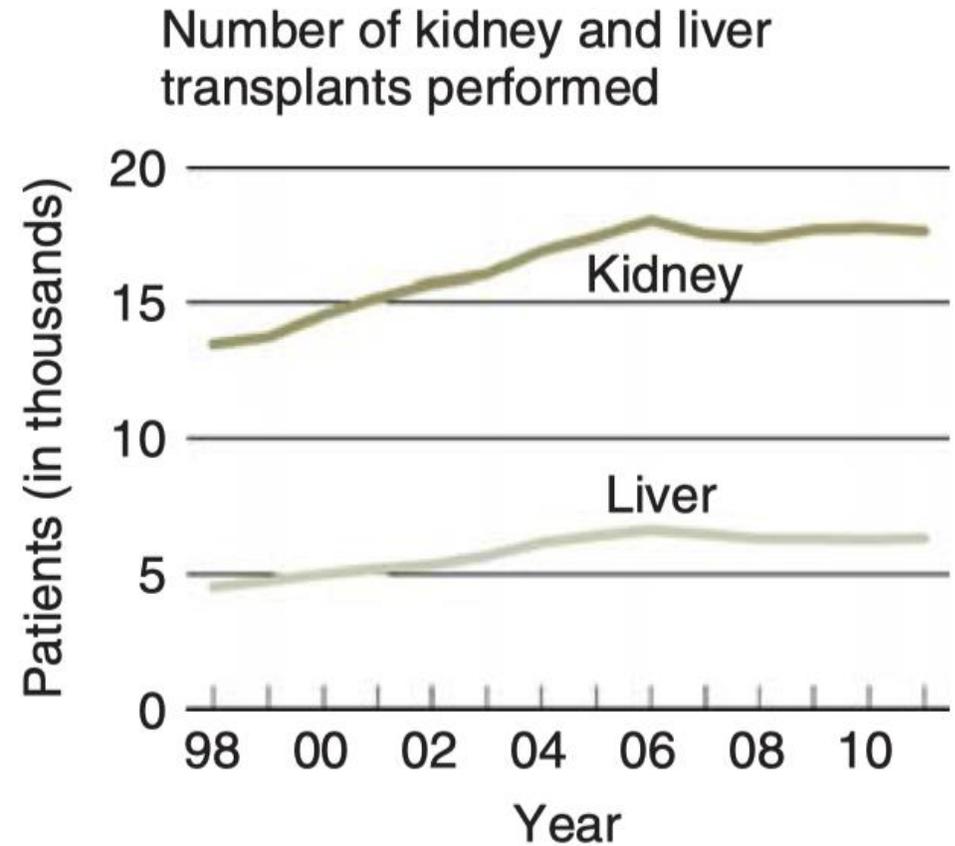
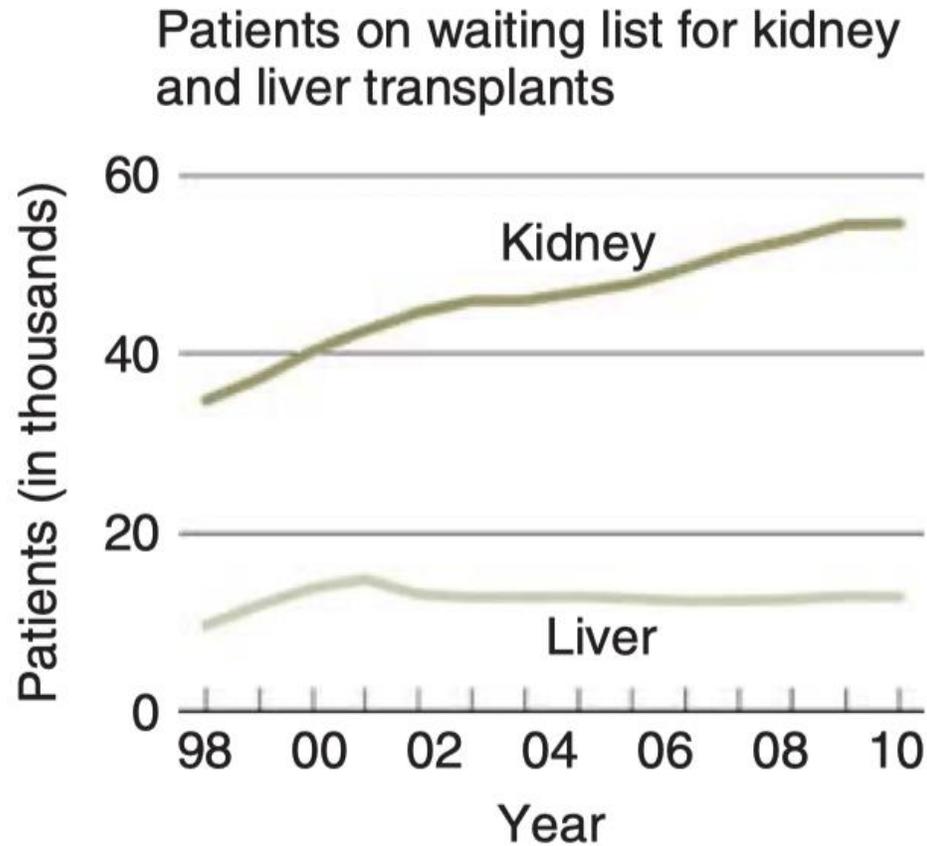


UNIVERSITÀ  
DEGLI STUDI  
DI TERAMO

**Corso di Laurea Magistrale in Biotecnologie Avanzate**  
**Corso di Laurea Magistrale in Reproductive Biotechnologies**  
**AA 2024-2025**

# **REQUIREMENTS FOR THE DEVELOPMENT OF BIOMEDICAL DEVICES**

# CHRONIC SHORTAGE OF ORGAN DONORS

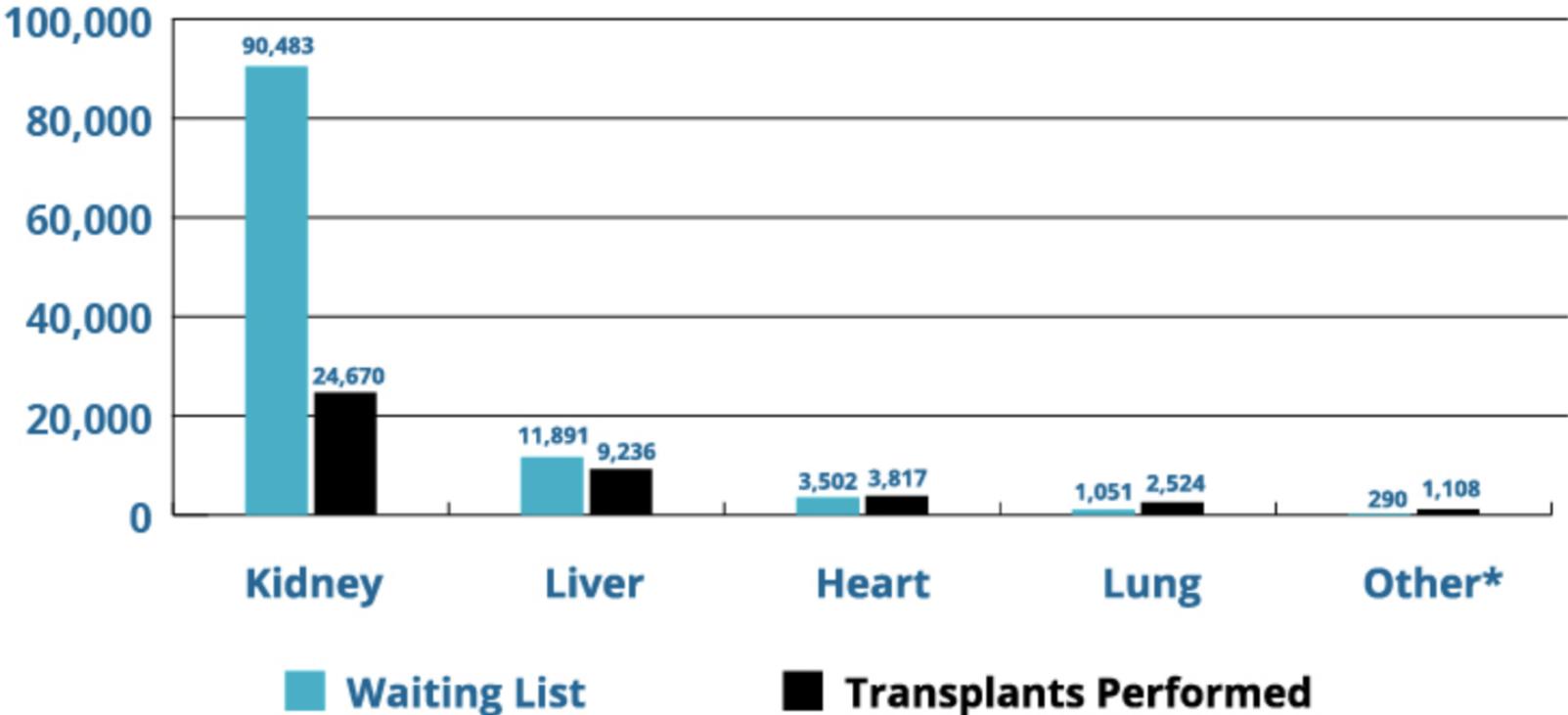


Donor Organ Shortage in the US—There is a chronic shortage of donor organs. The number of patients waitlisted for kidney and liver transplants is significantly higher than the number of donor organs available. Note—The data and analyses reported in the 2011 Annual Data Report of the Organ Procurement and Transplantation Network and the US Scientific Registry of Transplant Recipients have been supplied by the Minneapolis Medical Research Foundation and UNOS under contract with HHS/HRSA. The authors alone are responsible for reporting and interpreting these data; the views expressed herein are those of the authors and not necessarily those of the US Government.

# CHRONIC SHORTAGE OF ORGAN DONORS

## Patients on the Waiting List vs. Transplants Performed

By Organ in 2021



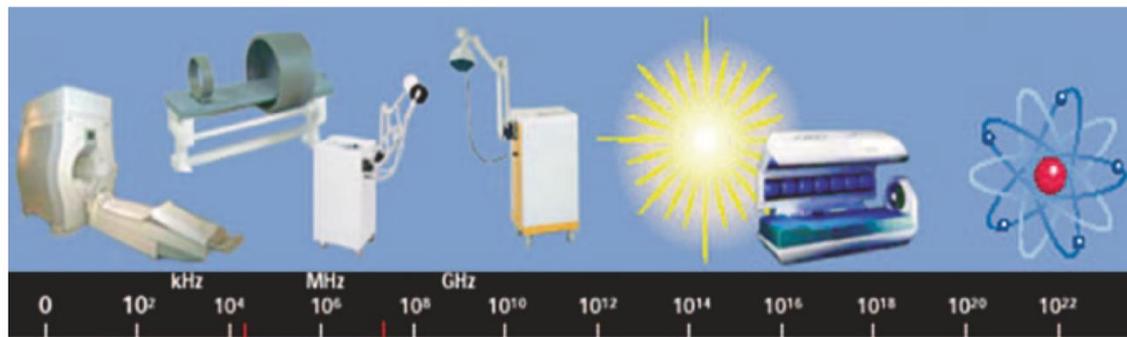
\*Other includes allograft transplants like face, hands, and abdominal wall.

# Medicine and Technology in Healthcare Services

Biomedical technologies are in general medical equipment used to diagnose and treat various diseases, ranging from simple devices to complex systems.

Medical devices are defined as articles that are intended to be used for medical purposes.

As internationally agreed, the biomedical instrumentation can be classified according to its use, i.e. the purpose it is used for. Thus we have:



diagnostic devices



therapeutic devices



rehabilitation devices

# CHALLENGES IN MEDICAL DEVICE INDUSTRY

## DESIGN CONTROL

learn to be successful  
in developing products that  
meets customer needs

Personalized Treatments

Reasonable Costs

improving the quality of treatment

**INNOVATION**

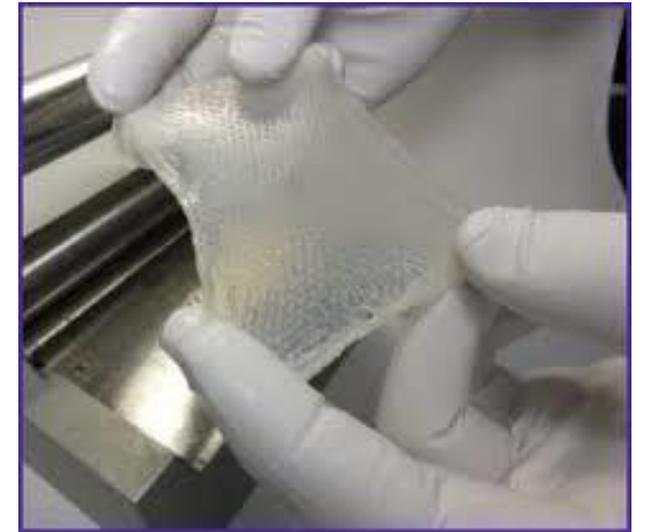
regenerative medical devices  
(scaffolds) and drug-eluting medical  
devices

understanding of biological processes,

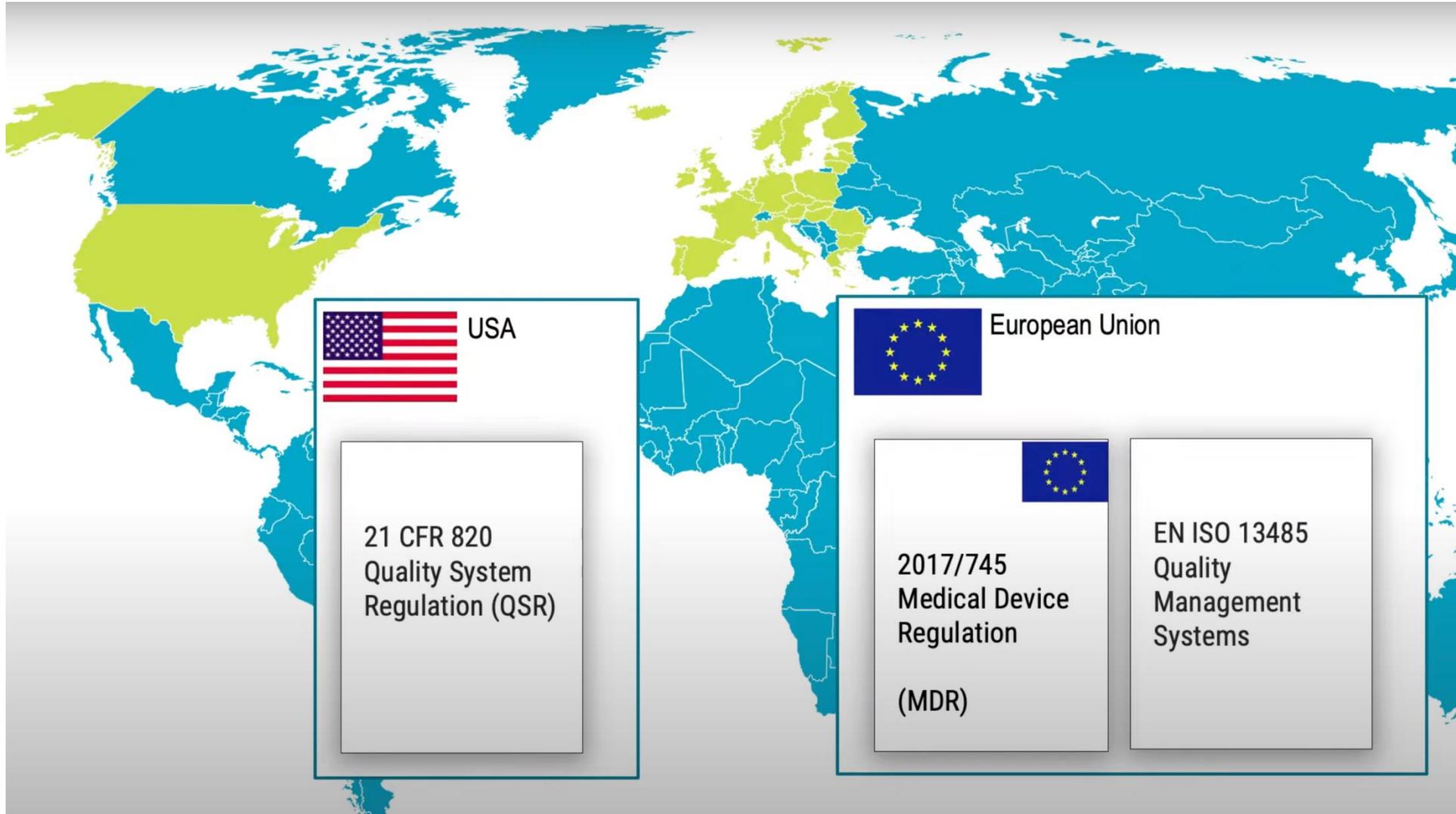
# INTENDED USE OF MEDICAL DEVICE

## Intended use

**Who?**  
**on Whom?**  
**What?**  
**Where?**  
**When?**



# QUALITY CONTROL REQUIREMENTS



# EU Harmonized Standards

## Examples

**ISO 13485 (QMS)**

**EN 980 (Labelling)**

**EN 10993 (Biological compatibility)**

**EN 11607 (Packaging)**

**EN 14155 (Clinical Evaluation)**

**ISO 14971 (Risk management)**

**EN 60601 (Medical electrical equipment)**

# BIOMEDICAL DEVICE

For the European market, medical devices are governed by a regulatory framework of three directives:

- 93/42/EEC: Medical Devices Directive (MDD)
- 90/385/EEC: Active Implantable Medical Device Directive (AIMDD)
- 98/79/EC: In vitro diagnostic medical devices (IVDMD)

According to them, a medical device is defined as **“any instrument, apparatus, appliance, software, material or other article, whether used alone or in combination, including the software intended by its manufacturer to be used specifically for diagnostic and/or therapeutic purposes and necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:**

- **diagnosis, prevention, monitoring, treatment or alleviation of disease,**
- **diagnosis, monitoring, treatment, alleviation of or compensation for an injury or handicap,**
- **investigation, replacement or modification of the anatomy or of a physiological process,**
- **control of conception,**

**and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.”**

# CLASSIFICATION OF BIOMEDICAL DEVICE

According to the EU, the classification of medical devices is based on the potential risks associated with the devices. This approach allows the use of a set of criteria that can be combined in various ways and be applied to a vast range of different medical devices and technologies. The classification depends on a series of factors including

- **duration:** how long the device is intended to be in continuous use,
- **invasiveness:** whether or not the device is invasive or surgically invasive,
- **type:** whether the device is implantable or active,
- **function:** whether or not the device contains a substance, which in its own right is considered to be a medicinal substance and has action ancillary to that of the device,

# CLASSIFICATION OF BIOMEDICAL DEVICE

According to “Classification rules”, they are divided as follows:

- Rules 1–4: for noninvasive devices,
- Rules 5–8: for invasive devices,
- Rules 9–12: for active devices,
- Rules 13–18: special rules for products that merit a higher classification than they might otherwise be assigned.

The devices are divided into four classes, ranging from low risk to high risk:

- Class I: low-risk medical devices,
- Class IIa: low-to-medium risk medical devices,
- Class IIb: medium-to-high-risk medical devices,
- Class III: high-risk medical devices.

## Classification - Medical Devices EU



Class I



- Wheelchairs
- Walking aids
- Stethoscopes
- Incision drapes
- Dental patient chairs

Class IIa



- Hearing aids
- Tubing intended for use with infusion pump
- Devices for storage of organs for transplantation
- Tracheal tubes
- Dental aspirator tips
- TENS devices
- Software apps

Less than 30 days

Class IIb



- Lung ventilators
- Dressings for severe wounds
- Urethral stents
- Urinary catheters for long term use
- Stents
- Peripheral vascular catheters

Longer than 30 days

Class III



- Breast implants
- Intra-aortic balloon pumps
- Spinal stents
- Prosthetic heart valves
- Central vascular catheters

# Categorization of medical devices

Medical devices shall be categorized according to the nature of body contact.

## Non-contacting medical devices

These include medical devices (or components) that have neither direct nor indirect contact with the body and where biocompatibility information would not be necessary.

Diagnostic software, an in vitro diagnostic device and a blood-collection tube are examples of non contact devices.

## Surface-contacting medical devices

a) Skin: Medical devices that contact intact skin surfaces only.

b) Mucosal membranes: Medical devices that contact intact mucosal membranes.  
prostheses and orthodontic devices.

c) Breached or compromised surfaces: Medical devices that contact breached or otherwise compromised body surfaces.

# Categorization of medical devices

Medical devices shall be categorized according to the nature of body contact.

## Externally communicating medical devices

- a) Blood path, indirect: Medical devices or components that do not necessarily contact the blood path directly but serve as conduits to deliver fluids into the vascular system.
- b) Tissue/bone/dentin:
  - Medical devices that contact tissue, bone or pulp/dentin systems.
  - Medical devices or components that do not necessarily directly contact tissue or bone but serve as conduits to delivery fluids to the tissue or bone.
- c) Circulating blood: Medical devices that contact circulating blood.

## Implant medical devices

- a) Tissue/bone:
  - Medical devices principally contacting bone.
  - Medical devices principally contacting tissue and tissue fluid.
- b) Blood: Medical devices principally contacting circulating blood in the cardiovascular system.

# Categorization of medical devices

Medical devices shall be categorized according to the duration of body contact.

## **5.3.1 Contact duration categories**

- a) Limited exposure (A) – medical devices whose cumulative sum of single, multiple or repeated duration of contact is up to 24 h.
- b) Prolonged exposure (B) – medical devices whose cumulative sum of single, multiple or repeated contact time is likely to exceed 24 h but not exceed 30 d.
- c) Long-term exposure (C) – medical devices whose cumulative sum of single, multiple or repeated contact time exceeds 30 d.

# CLASSIFICATION OF BIOMEDICAL DEVICE: EXAMPLES

**As an example, a manufacturer willing to classify a silicone tracheal stent must consider the rules associated with an invasive medical device (Rules 5–8):**

- **Rule 5** (*invasive in body orifice or stoma—not surgically*)

If it is for transient use

If it is for short-term use

*However*, if it is for oral cavity, ear canal, or nasal cavity

If it is for long-term use

*However*, if it is for oral cavity, ear canal, or nasal cavity

and it will not be absorbed by the mucous membrane

If it is connected to an active medical device in class IIa or higher

Class I

Class IIa

Class I

Class IIb

Class IIa

Class IIa

- **Rule 6** (*surgically invasive—transient use*)

If it is surgically invasive for transient use

If it is used to control/diagnose/monitor/correct a defect of the heart or the central circulatory system through direct contact

If it is used for the central nervous system (direct contact)

If it is a reusable surgical instrument

If it is used to supply energy or ionizing radiation

If it has a biological effect (mainly or wholly absorbed)

If it is intended to administer medicines in a potentially hazardous manner

Class IIa

Class III

Class III

Class I

Class IIb

Class IIb

Class IIb

- Class I: low-risk medical devices,
- Class IIa: low-to-medium risk medical devices,
- Class IIb: medium-to-high-risk medical devices,
- Class III: high-risk medical devices.

# CLASSIFICATION OF BIOMEDICAL DEVICE: EXAMPLES

- **Rule 7** (*surgically invasive—short-term use*)

If it is surgically invasive for short-term use	Class IIa
If it is used to control/diagnose/monitor/correct a defect of the heart or the central circulatory system through direct contact	Class III
If it is used for the central nervous system (direct contact)	Class III
If it is used to supply energy or ionizing radiation	Class IIb
If it has a biological effect (mainly absorbed)	Class III
If it undergoes chemical changes in the body, or if it administers medicines (not in teeth)	Class IIb

- **Rule 8** (*surgically invasive—long-term use or implantable devices*)

If it is surgically invasive for long-term use or if it is an implantable device	Class IIb
If it has to be placed in teeth	Class IIa
If it has to be in contact with the heart or central circulatory/nervous system	Class III
If it has a biological effect (or mainly absorbed)	Class III
If it undergoes chemical changes in the body, or if it administers medicines (not in teeth)	Class III
For specific derogation: breast implants, hip, knee, and shoulder joint replacements	Class III

- **Duration:** the silicone stent will be placed inside the trachea for more than 30 day; therefore, the device is for long-term use (RULE ???).

- **Invasiveness:** the stent will be totally introduced inside the orifice of the trachea using a bronchoscope and anesthesia (surgical operation); therefore, the device is considered an implantable device (RULE ???).

- Class I: low-risk medical devices,
- Class IIa: low-to-medium risk medical devices,
- Class IIb: medium-to-high-risk medical devices,
- Class III: high-risk medical devices.

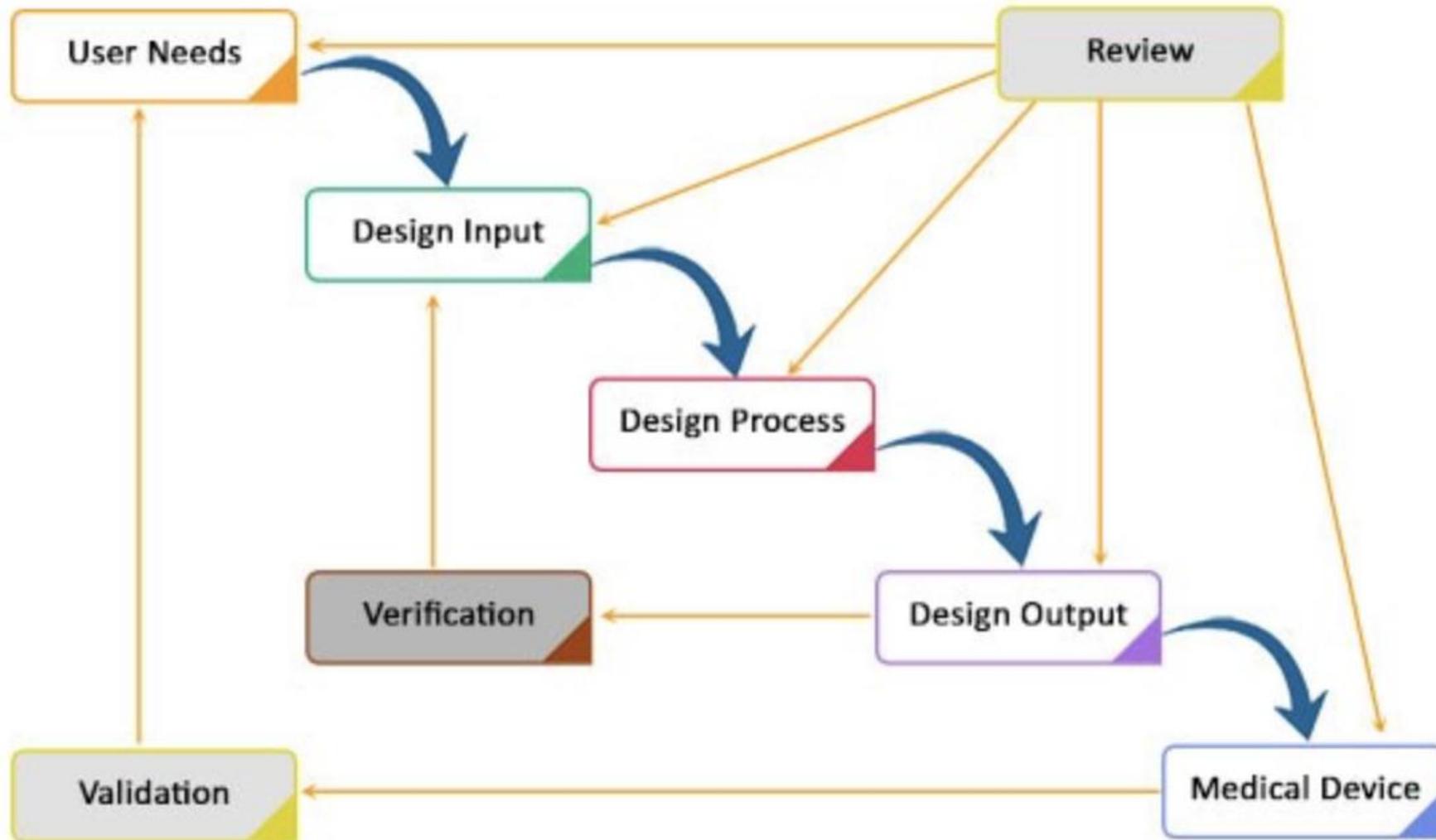
# BIOMEDICAL DEVICE REQUIREMENTS

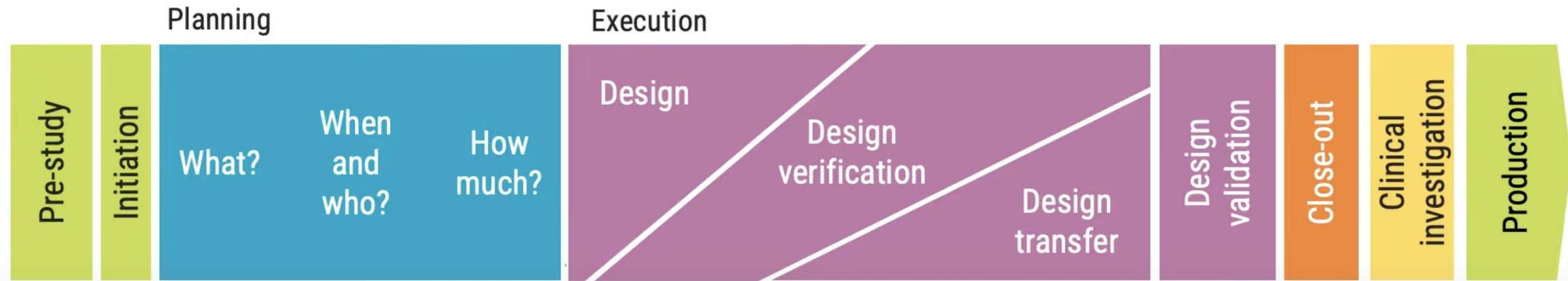
Based on clinical experience, there are several biological, mechanical, chemical, and physical requirements for biomaterials that should be targeted to develop more efficient and adequate medical devices including foreign body reaction (due to wear fibrils), stress shielding, biocompatibility, bioactivity, inductive properties, etc. A description of the major requirements is listed here:

- **Safety**: it is the most important requirement for medical devices. They must be safe and not show any toxicity. Therefore, corrosion-resistant materials should be used.
- **Durability**: there is a need to improve the durability of materials and wear resistance in order to increase product life and reduce medical interventions due to replacement or fatigue problems.
- **Mechanical Compatibility**: this is a key characteristic for multiple purposes such as to avoid stress shielding.
- **Biodegradability**: in order to increase biocompatibility, reduce immune reactions, and avoid retrieval, there is a need to develop biodegradable materials.
- **Biofunction**: to improve the performance of several medical devices, there is a need to promote tissue formation (e.g., fixation of devices in bone), to promote adhesion of soft tissue (e.g., fixation of soft tissue), to prevent thrombus (e.g., inhibition of platelet adhesion), to avoid infections (e.g., inhibition of biofilm formation), to reduce magnetic susceptibility (e.g., avoid artifacts in MRI), etc.

**Finally, a major concern in the medical device field is infection. Bacteria often colonize the surface of medical devices developing a biofilm that compromises not only the functionality and performance of the device but also the patient's health. For these cases, removal of the infected device is frequently the only option.**

# “Waterfall” Design Process





# Verification and Validation

Design **Verification** – Evidence that the manufacturer **made the product right**

Design **Validation** – Evidence that the manufacturer **made the right product**

# RISK MANAGEMENT PROCEDURES

Risk management procedures for medical devices are enforced under internationally accepted compliance standard ISO 149711:2007 Medical Devices – “Application of Risk Management to Medical Devices”. Apart from this, risk management policies need to be incorporated across all the stages of medical device design and development and should be also associated with design control aspects as well.

**WHAT IS THE DEFINITION OF RISK?**

**Free from Risk**

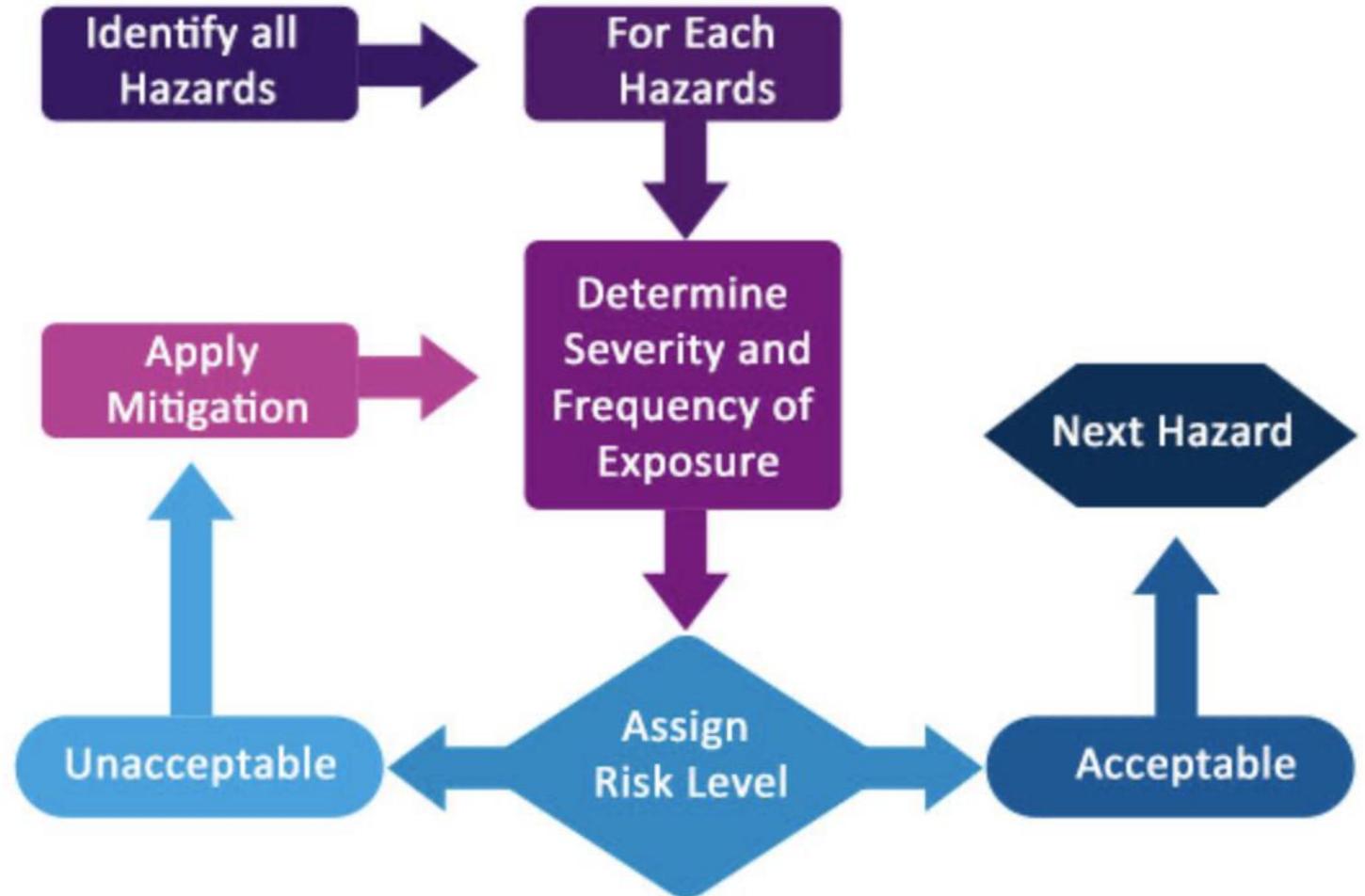
**Freedom from Unacceptable Risk**

# RISK MANAGEMENT PROCEDURES

It is a process of **identifying, controlling and preventing the failure that may cause hazards** to users.

There are certain hazards that must be evaluated:

- **Raw materials and wastes:** toxicity, flammability, and reactivity of material
- **Environmental factors:** sensitivity to temperature and humidity and more
- **Mechanical or electronic hazards**



# RISK MANAGEMENT PROCEDURE AND PLAN

SOP-008  
Risk management  
procedure

1(5)



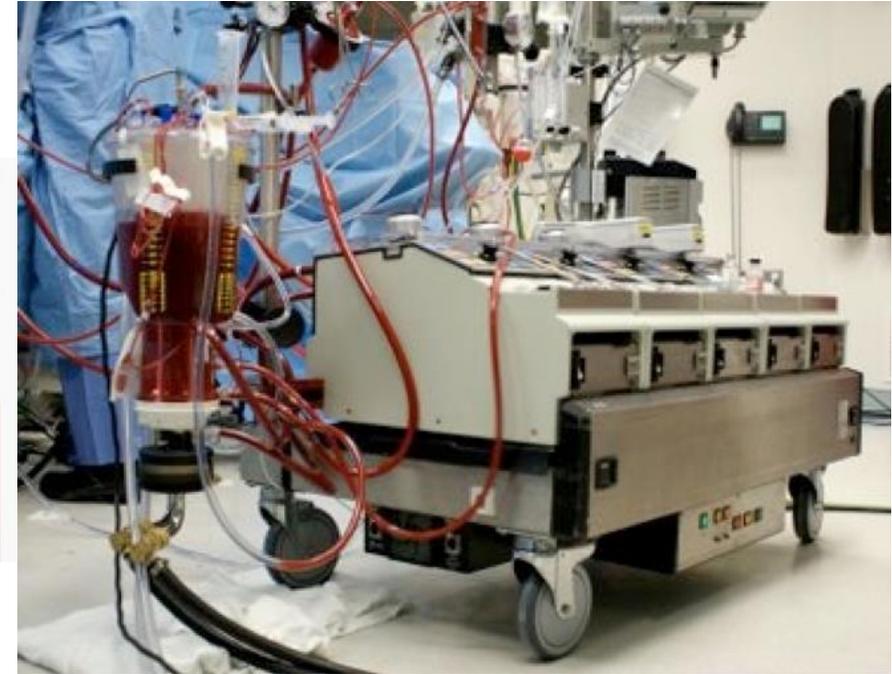
Risk  
management plan  
Product A

1(5)



# RISK ANALYSIS AND RISK EVALUATION

Risk analysis - HEART LUNG MACHINE						Risk eval.
Hazard	Reasonably foreseeable sequence or comb. of events	Hazardous situation	Harm	Po	S	Risk acc?
Electricity	Production personnel accidentally connects live cable to ground on device making the device live too.	User is exposed to electricity.	Death	3	5	N ACC



# RISK ACCORDING TO ISO 14971

## Risk

combination of the probability of occurrence of harm and the severity of that harm.

Probability of Occurrence  
of Harm (Po)



Severity (S)



=

Risk



# RISK ACCORDING TO ISO 14971

## Poccurence (per use)

Definition	Value
Improbable	1
Remote	2
Occasional	3
Probable	4
Frequent	5

## Severity

Rating	Value
Negligible	1
Minor	2
Serious	3
Critical	4
Catastrophic	5

		Severity				
Probability		1	2	3	4	5
1	ACC	ACC	ACC	ACC	ACC	ACC
2	ACC	ACC	ACC	ACC	ACC	N ACC
3	ACC	ACC	ACC	N ACC	N ACC	N ACC
4	ACC	ACC	N ACC	N ACC	N ACC	N ACC
5	ACC	N ACC	N ACC	N ACC	N ACC	N ACC

# RISK CONTROL

## Risk control

Risk control options analysis	Risk control measure	Verification of effectiveness	Impl.?	R-Po	R-S	Risk acc?
The product cannot be made inherently safe by design since electricity is required. Protective measures can be applied.	Length of cable X1 is designed to rule out incorrect connection. Final test shall include electrical safety test that will discover error.	Analyse cable connection errors. Review final test instruction. Perform fault injection test. See reports 1392-1, 1398.	Yes	1	5	ACC

# RISK MANAGEMENT

Was the risk management implemented appropriately?

Risk management plan  
Product A



Is the overall residual risk acceptable?



Are methods in place for collection and review of production and post-production info?



Risk management  
report  
Product A



1(3)

# RISK MANAGEMENT FILE

Risk management file  
Risk mngt plan  
131982-1  
Hazard trace matrix  
139182-1  
Risk management report  
1397122-1

1(1)



# BIOMEDICAL DEVICE: EXAMPLES



*BioRipar*<sup>®</sup>

MEMBRANA DI COLLAGENE  
DA DERMA PORCINO

Il dispositivo medico è una membrana di collagene ottenuta dal derma estratto da cute porcina, sottoposto ad un trattamento chimico multifasico, ideato e sviluppato in ASSUT EUROPE S.p.A. Il procedimento di lavorazione è finalizzato alla completa distruzione delle cellule ed alla successiva rimozione dei residui cellulari e proteici inquinanti, tra i quali acidi nucleici, cheratina e grassi, non alterando la struttura tridimensionale del collagene le sue proprietà biomeccaniche.

Il DM è disponibile in due forme:

1. una forma composta dal collagene di tipo I e III, ed elastina, ottenuta dalla rimozione dell'ipoderma e dell'epidermide, lasciando lo strato centrale di derma
2. una forma rinforzata con la membrana basale, composta da collagene di tipo IV e VII

Il dispositivo agisce come matrice per la germinazione dei fibroblasti, la formazione di nuovi tessuti e vasi sanguigni. Contemporaneamente alla creazione di tessuti nuovi si ha una graduale degradazione del collagene di derma.

## CARATTERISTICHE DEL PRODOTTO

La caratteristica più importante del Bioripar Derma Porcino è la sua struttura di collagene (di tipo I e III), che ne garantisce la stabilità risultando comunque morbida e flessibile. La membrana è facilmente suturabile.

Dopo la sua applicazione, la matrice di collagene ripara le superfici danneggiate. L'organismo reagisce all'introduzione di collagene iniziando il processo di riparazione dei tessuti danneggiati: inizia a liberare un gran numero di citochine, fattori di crescita, e sostituisce gradualmente il materiale impiantato con i tessuti sani.

BIORIPAR - DERMA PORCINO

# BIOMEDICAL DEVICE: EXAMPLES

**ASSUFIL®**



Sutura sintetica intrecciata e rivestita a medio assorbimento (60-90 giorni)

Braided and coated synthetic suture mid term absorption (60-90 days)

Sutura sintética trenzada y recubierta de absorción media (60-90 días)



**MOLECOLA**

Polimero di acido glicolico.

**TIPO DI FILO**

Sutura sintetica assorbibile intrecciata (monofilamento nei calibri: USP 10/0 - 9/0; EP 0,2 - 0,3) e rivestita.

**COLORE**

Viola (D&C Viola n.2=C.I. 60725) o non colorato.

**DIAMETRI  
ED AGHI STANDARD**

Diametri EP da 0,2 a 6; diametri USP da 10/0 a 3&4.

L'Assufil viene assemblato con aghi atraumatici in acciaio inox AISI 300 o AISI 400;

possono anche essere del tipo "a distacco controllato" per permettere il distacco dell'ago con un semplice movimento del porta-ago.

**RESISTENZA TENSILE**

Dopo 7 gg dall'impianto permane ~ 90% della resistenza tensile, dopo 14 gg ~ 75% della resistenza tensile, dopo 21 gg ~ 50% della resistenza tensile, dopo 28 gg ~ 30% della resistenza tensile.

**ASSORBIMENTO**

Completo entro 60-90 giorni dall'impianto.

**INDICAZIONI**

In chirurgia generale, toracica, ortopedica, ginecologica, oftalmica, neurologica, nella riapprossimazione dei tessuti molli e/o ogni volta che si richieda una sutura chirurgica assorbibile.

# COMPONENT AUTHORITIES

## Who watches you?



Medicines and Healthcare  
Products Regulatory Agency, MHRA (UK)  
Medical Products Agency (SE)  
Danish Medicines Agency (DK)

### Notified Bodies

The manufacturer pays the notified  
body to examine the quality  
management system/devices  
(often 1/year).



Food and Drug Administration, FDA (US)

