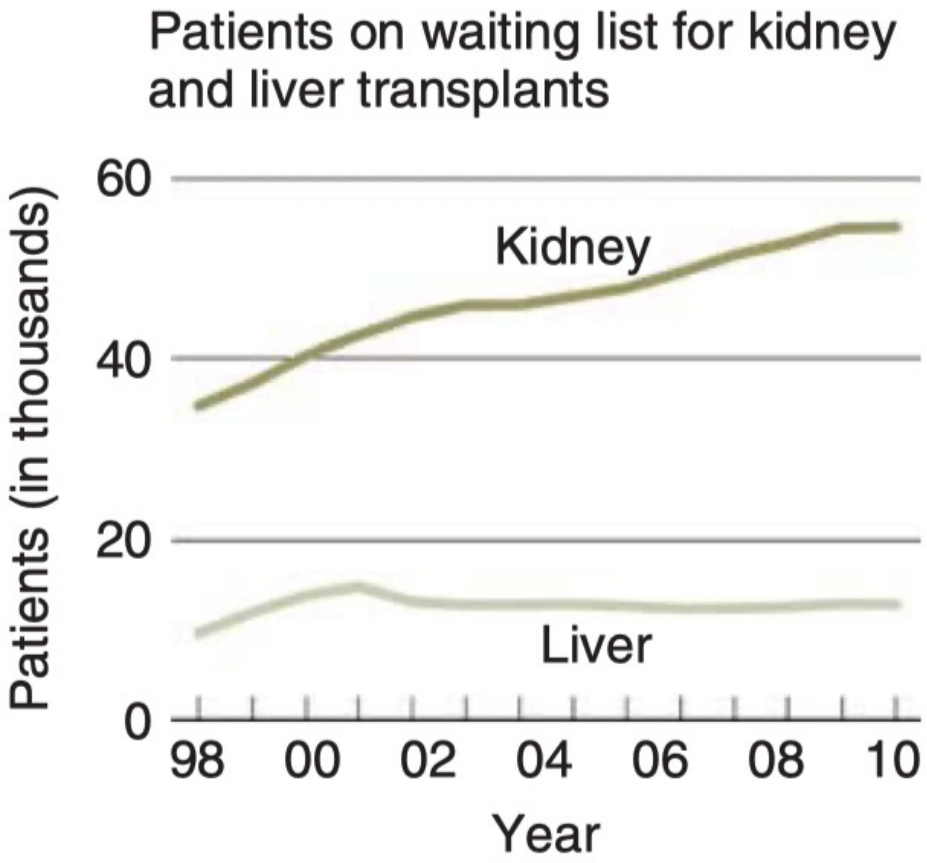
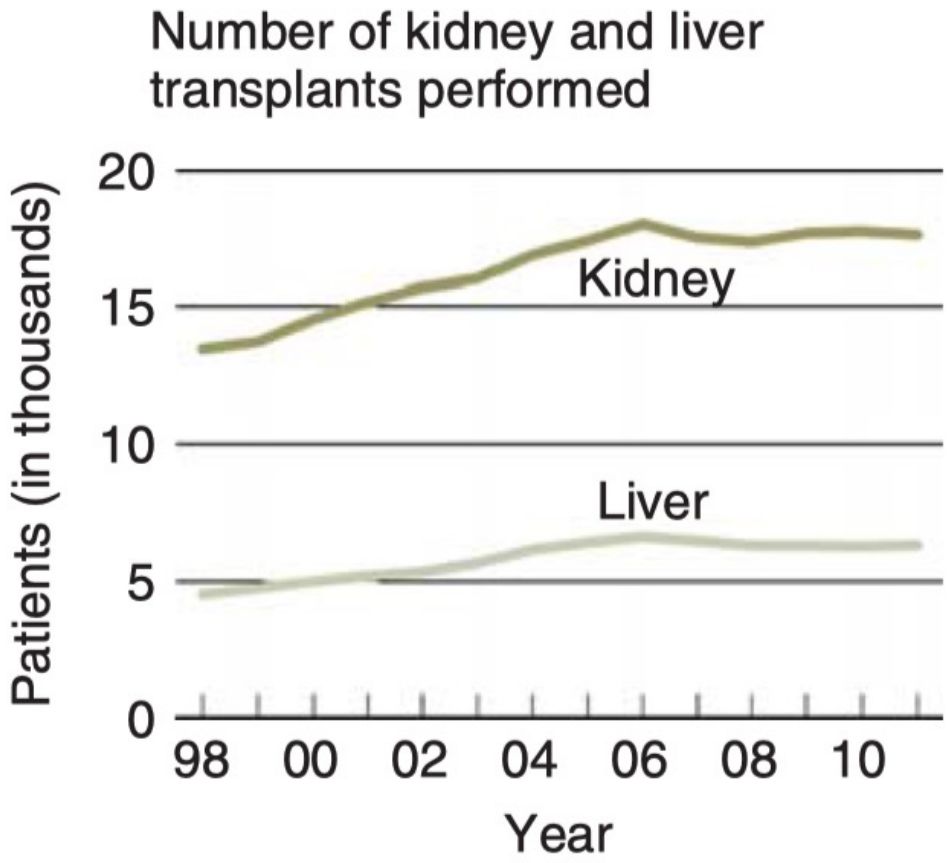
UNIVERSITÁ
DEGLI STUDI
DI TERAMO

Corso di Laurea Magistrale in Biotecnologie Avanzate
AA 2021-2022

REQUIREMENTS FOR THE DEVELOPMENT OF BIOMEDICAL DEVICES

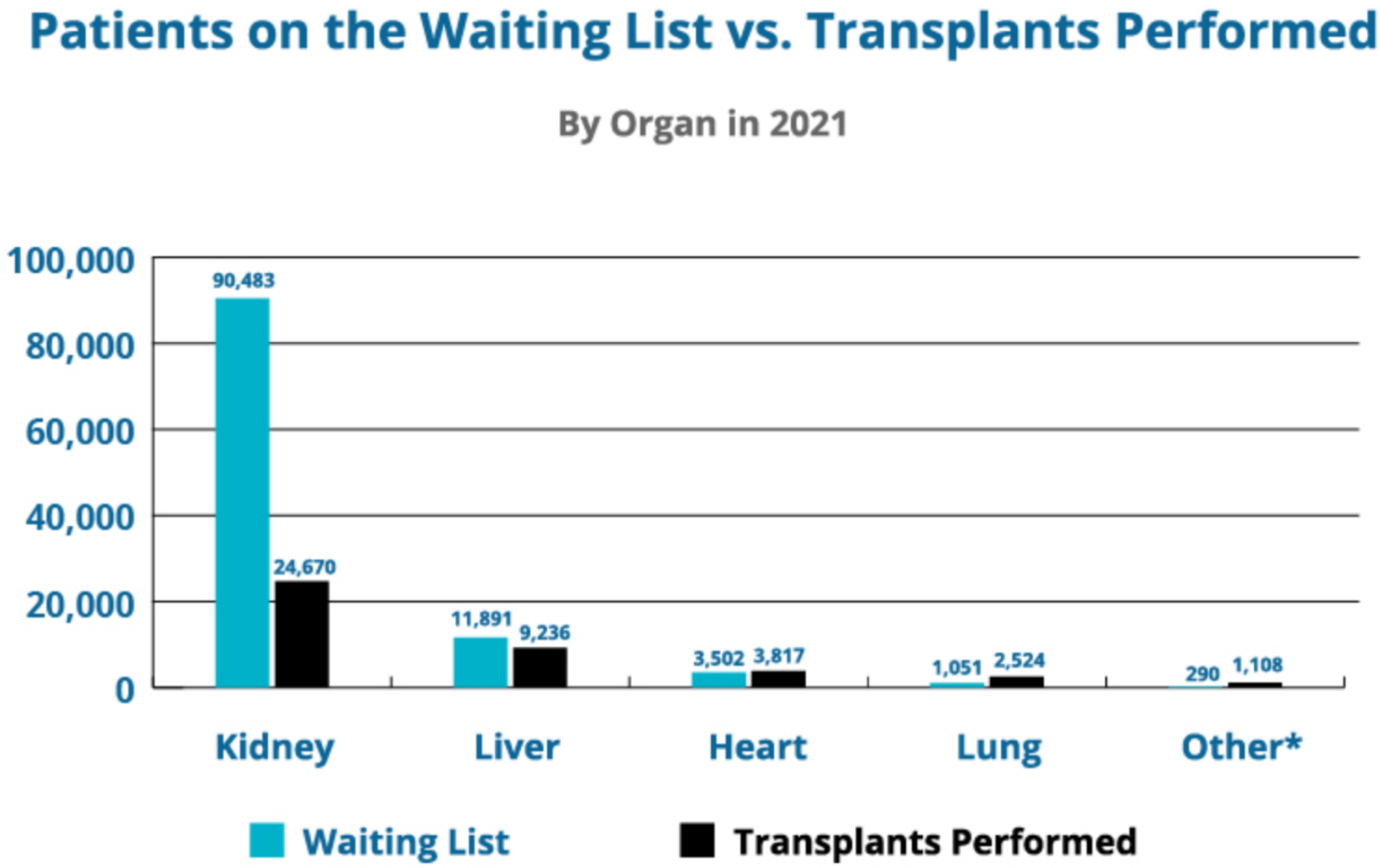
CHRONIC SHORTAGE OF ORGAN DONORS





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



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

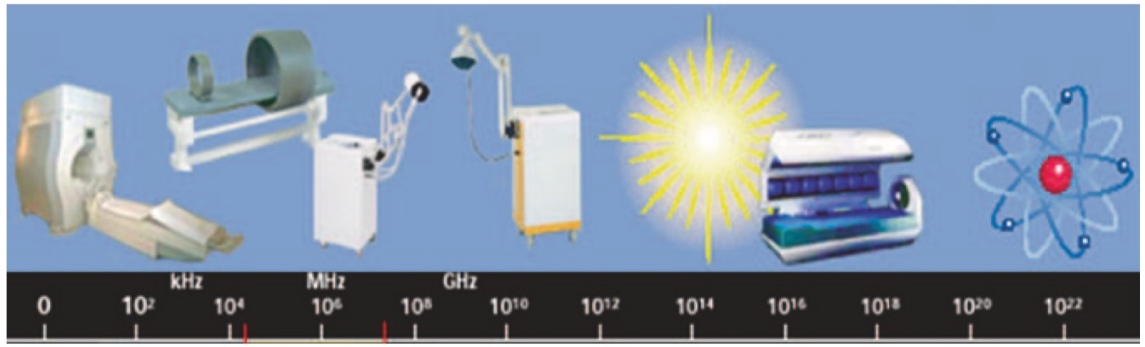
https://www.organdonor.gov/learn/organ-donation-statistics

Medicine and Technology in Healthcare Services

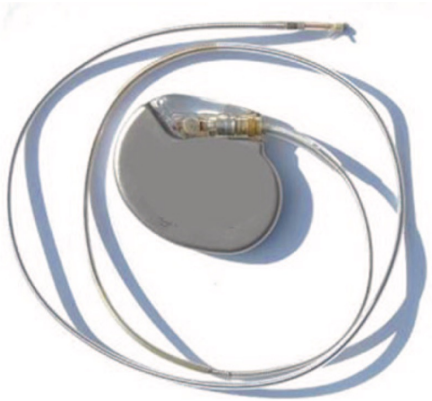
Biomedical technologies are in general medical equipment used to diagnose and treat various diseases, ranging from simple devices to complex systems.

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

Personalized Treatments

Reasonable Costs

INNOVATION

improving the quality of treatment

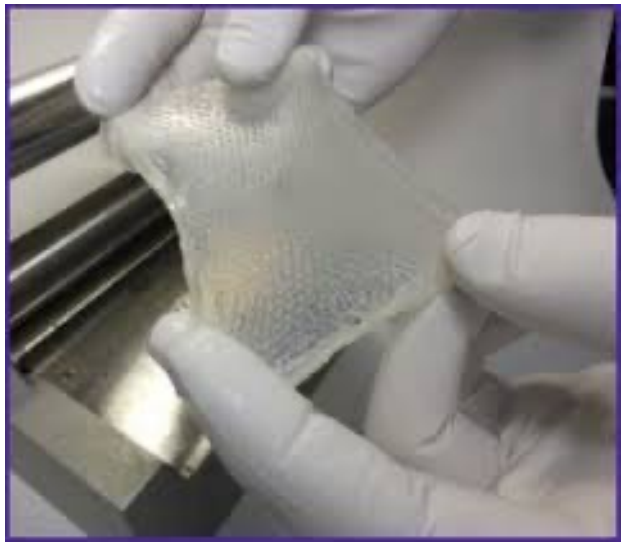
regenerative medical devices (scaffolds) and drug-eluting medical devices

understanding of biological processes,

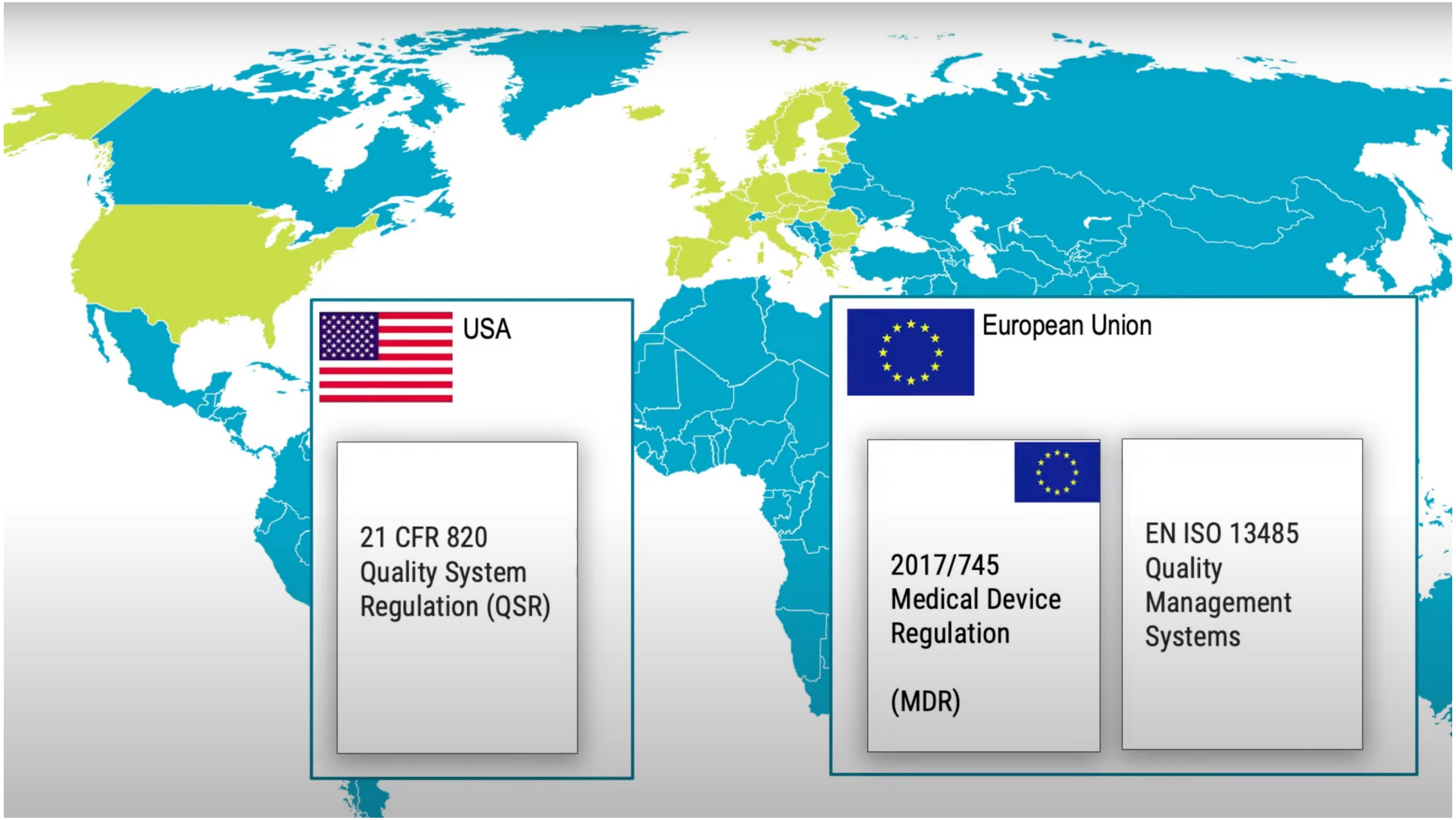
INTENDED USE OF MEDICAL DEVICE

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,

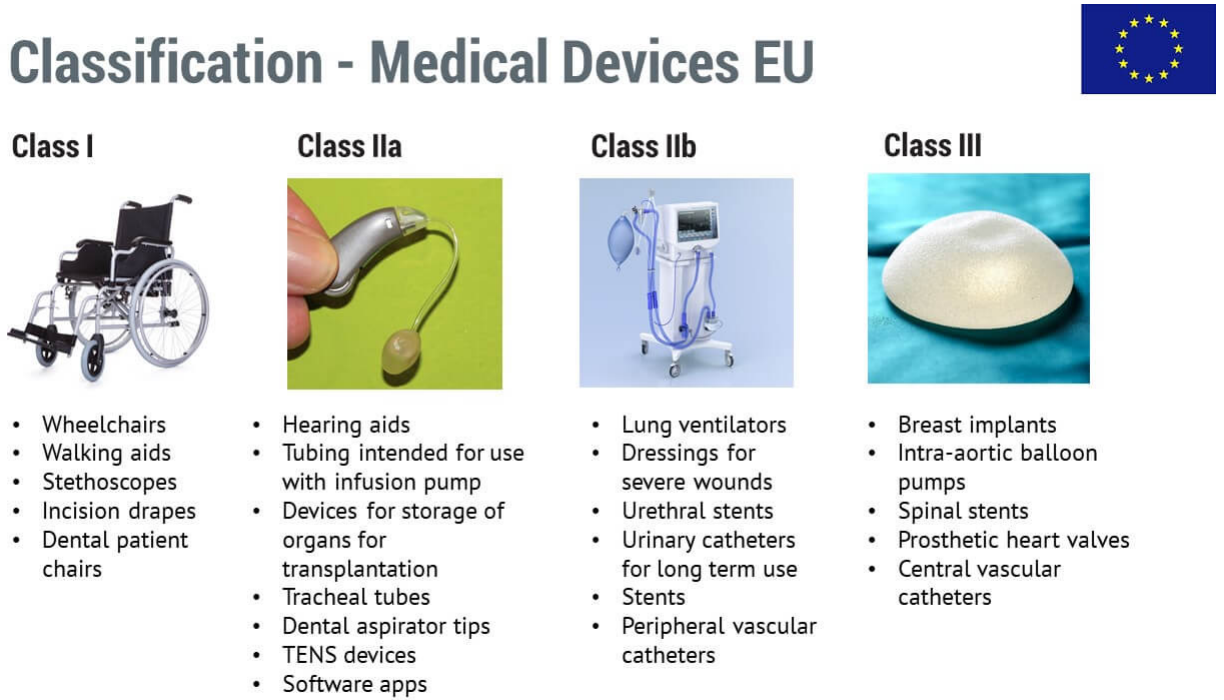
CLASSIFICATION OF BIOMEDICAL DEVICE

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 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	Class I
If it is for short-term use	Class IIa
However, if it is for oral cavity, ear canal, or nasal cavity	Class I
If it is for long-term use	Class IIb
However, if it is for oral cavity, ear canal, or nasal cavity and it will not be absorbed by the mucous membrane	Class IIa
If it is connected to an active medical device in class IIa or higher	Class IIa

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

If it is surgically invasive for transient 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 a reusable surgical instrument	Class I
If it is used to supply energy or ionizing radiation	Class IIb
If it has a biological effect (mainly or wholly absorbed)	Class IIb
If it is intended to administer medicines in a potentially hazardous manner	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.

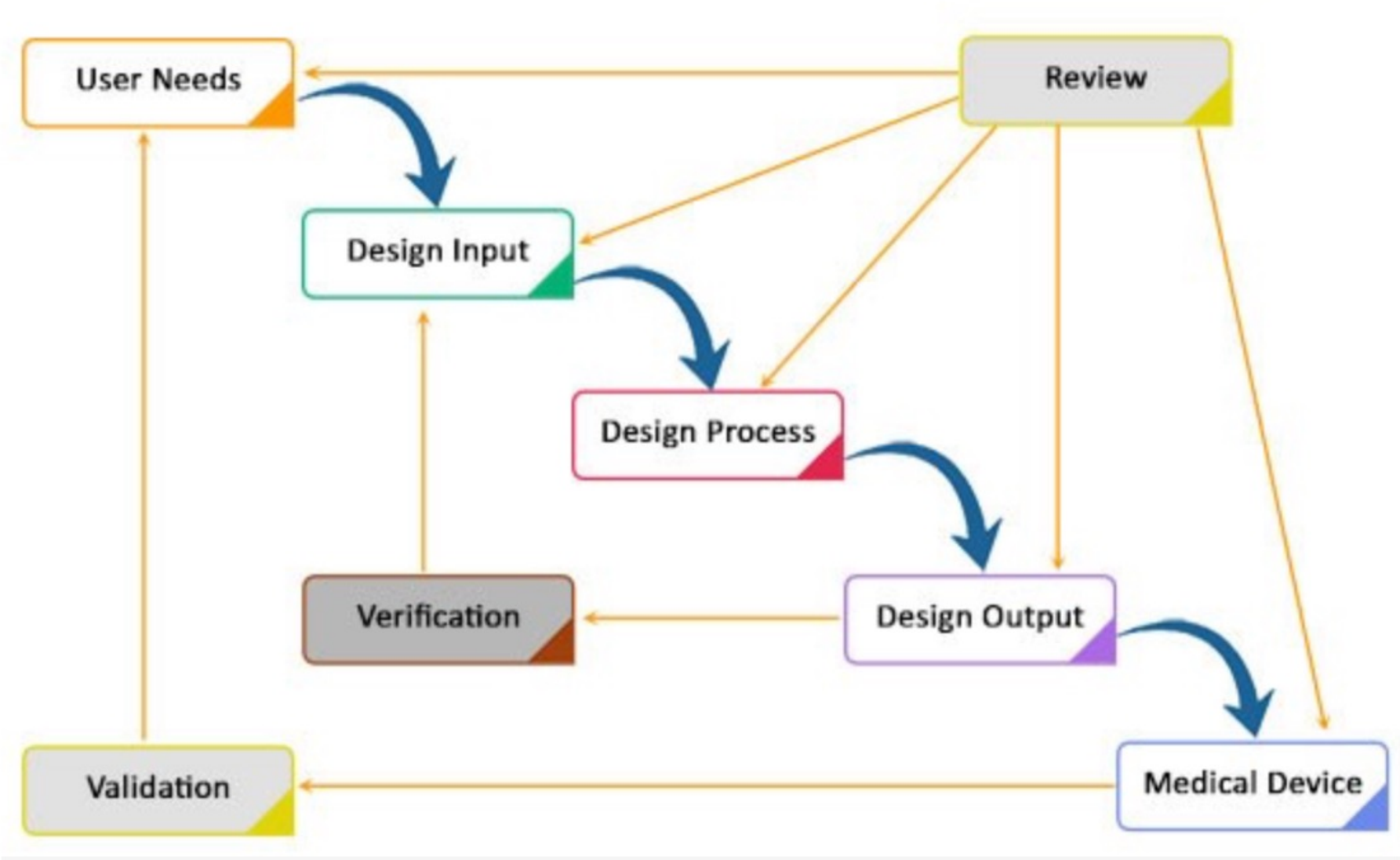
BIOMEDICAL DEVICE REQUIREMENTS

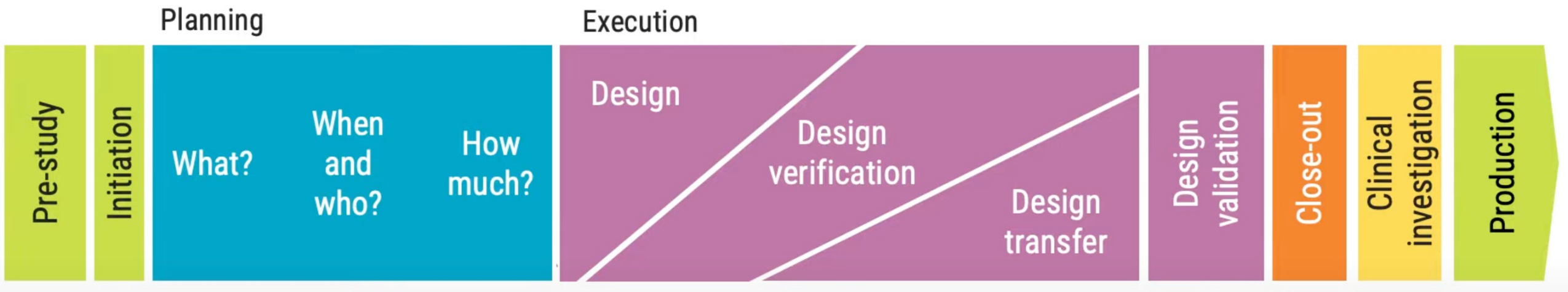
Based on clinical experience, there are several biological, mechanical, chemical, and physical requirements for biomaterials that should be targeted to develop more efficient and adequate medical devices including foreign body reaction (due to wear fibrils), stress shielding, biocompatibility, bioactivity, 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




Planning
Execution
Pre-study
Initiation
What?
When and who?
How much?
Design
Design verification
Design transfer
Design validation
Close-out
Clinical investigation
Production

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

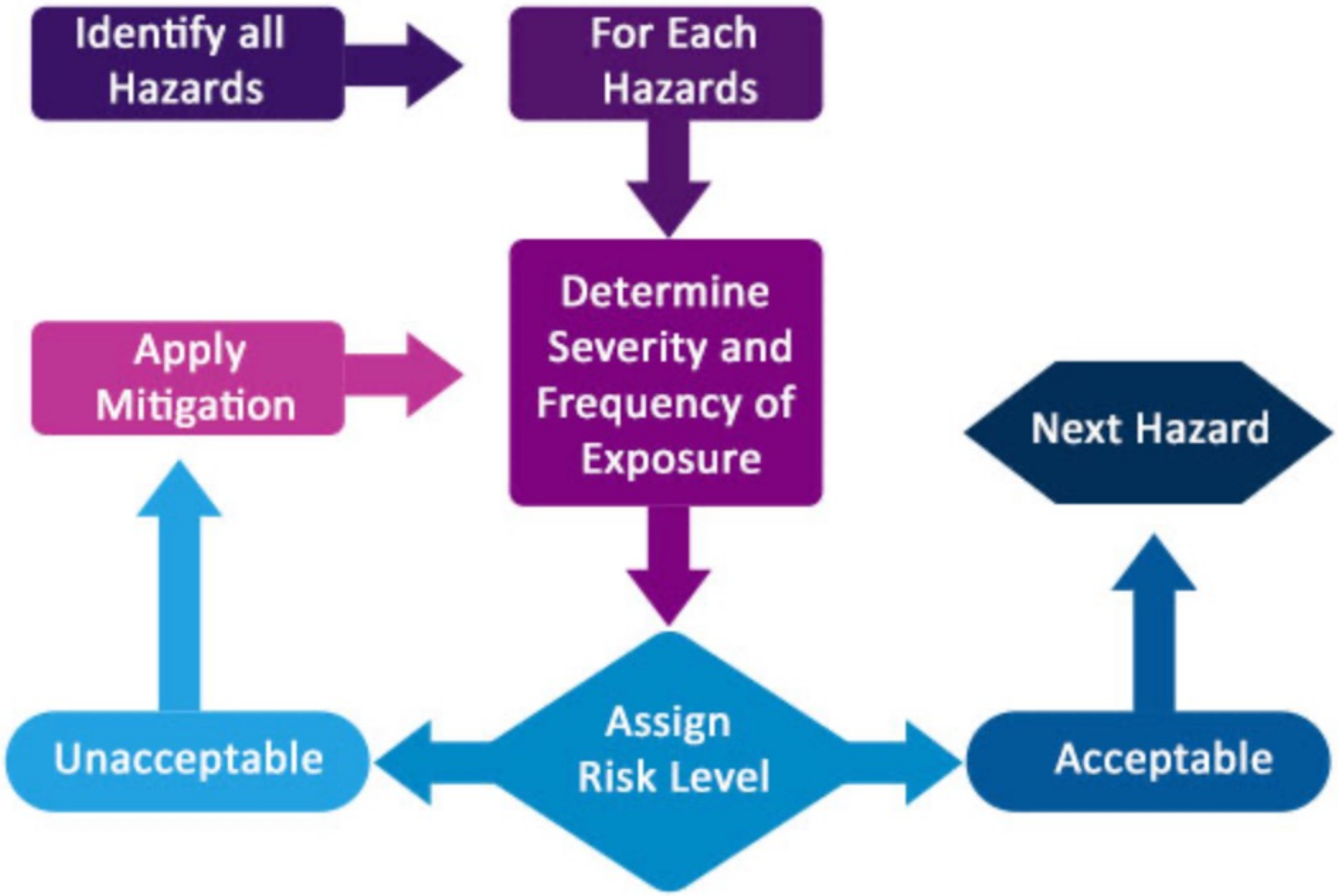
Freedom from Unacceptable Risk

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:

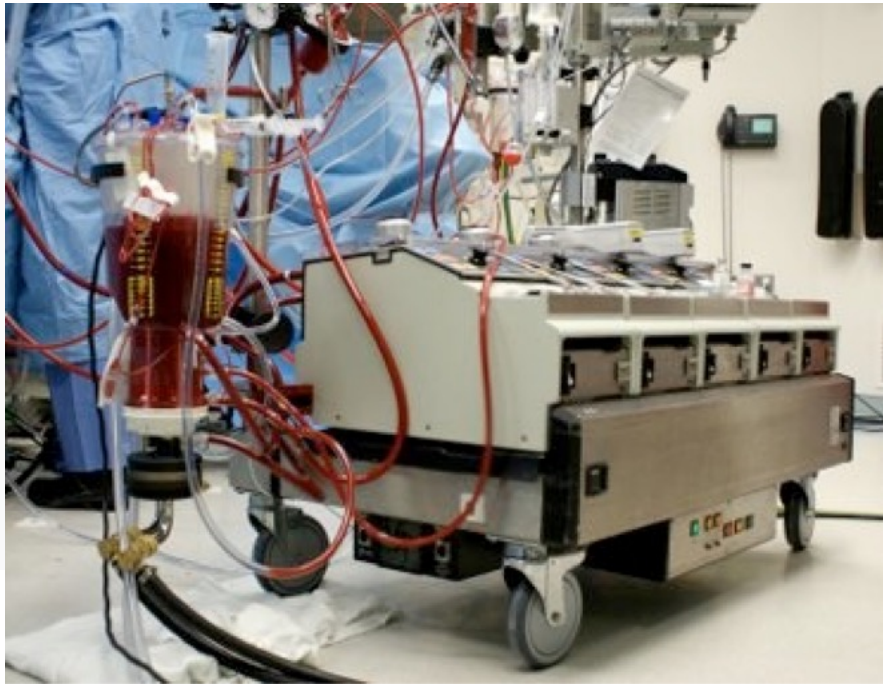
- **Raw materials and wastes:** toxicity, flammability, and reactivity of material
- **Environmental factors:** sensitivity to temperature and humidity and more
- **Mechanical or electronic hazards**



RISK MANAGEMENT PROCEDURE AND PLAN

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.

RISK ACCORDING TO ISO 14971

Poccurence (per use)

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

Severity

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

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

RISK CONTROL

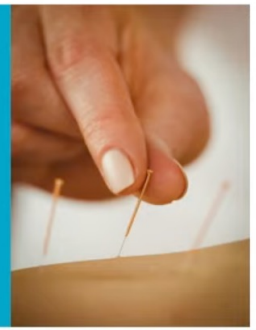
Risk control						
Risk control options analysis	Risk control measure	Verification of effectiveness	Impl.?	R-Po	R-S	Risk acc?
The product cannot be made inherently safe by design since electricity is required. Protective measures can be applied.	Length of cable X1 is designed to rule out incorrect connection. 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®

MEMBRANA DI COLLAGENE
DA DERMA PORCINO

BIORIPAR - 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.

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-aghi.
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)

Food and Drug Administration, FDA (US)

Notified Bodies

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