Medical Devices
An Introduction

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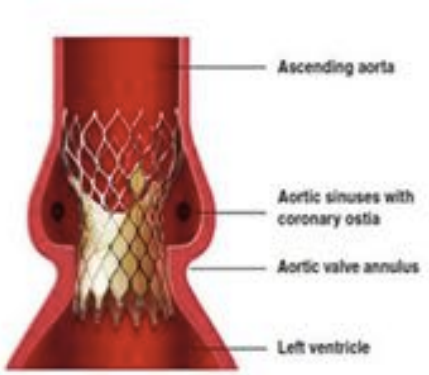
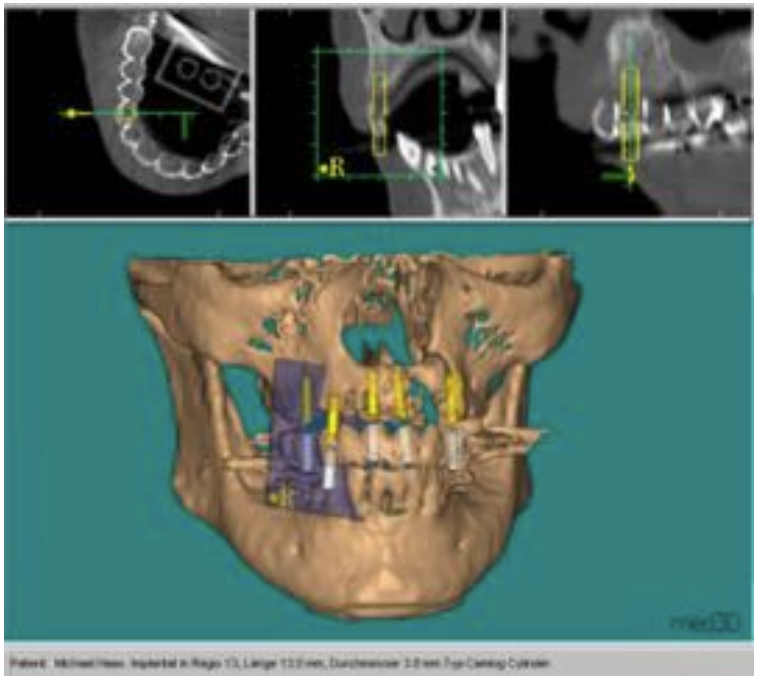
What do they have in common?

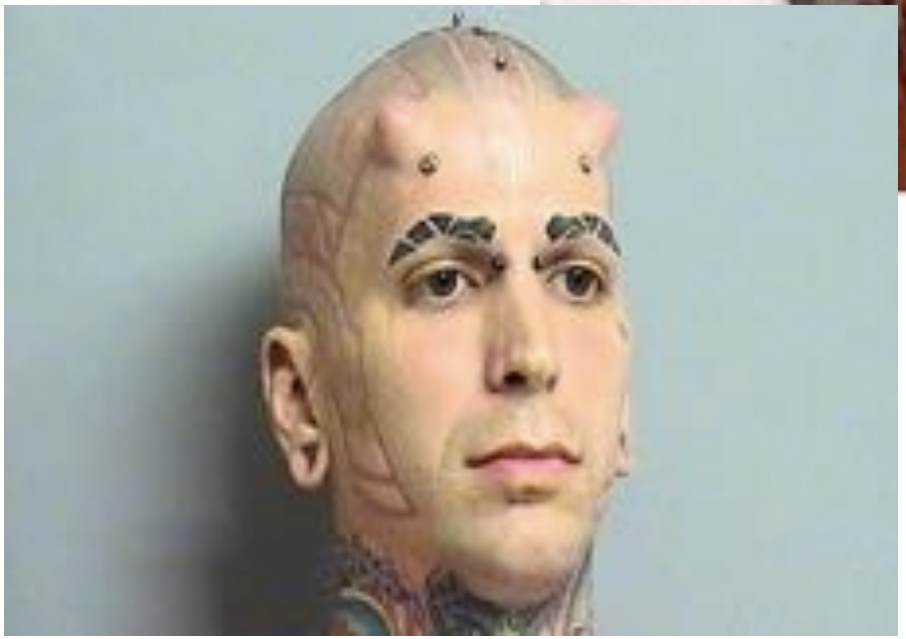


And now?


Tubing connect
Blood gas moni
Pressure monit
Water heater
ECMO pump
Artificial lung
Back-up batter




Cosplay



Some more examples of Medical Devices

- Band aids
- Incontinence pads
- ECG
- RMI
- Heart valves from bovine or porcine tissue
- Knee joints
- Hearing aids
- Vessel mesh
- Bone fillers
- Dental implants
- Bone screws both removable or permanent
- Defibrillators
- IV sets
- Syringes
- Eye drops (artificial tears)
- ….and on

Where Medicine and Engineering meet

- A Medical Device is an object destined to medical purposes on human patients
- It is designed and manufactured by the industry
- It is marketed to the general public or to health organizations according to (modified) market rules
- The medical devices industry is one of the leading innovation industries

Multiple sides of the same object

- Any given medical device must comply to multiple rules:
  - engineering of design
  - efficiency of industrialization
  - cost-profit on the market
  - multiple regulations aiming to ensure safety
  - clinical efficacy
- It is a challenge to designers
  - Medical state of the art
  - Industry standards
  - Innovation

The first step: a shared definition

- A Medical Device is identified by means of its INTENDED PURPOSE
- Intended to treat, prevent or control physiological characteristics of a living being
  - Disease
  - Handicap
  - Conception
  - Anatomy
  - ……

Comments

- Use on **humans** (or animals on a lower grade of regulation)
- Intended to have **a MEDICAL purpose**, excluding devices intended for
  - Esthetical purposes
  - Research not aimed to marketing of the device
- Multiple ways of **interacting with the human body**
  - Implant to NO corporeal interaction (medical SW)
  - Temporary or permanent
  - Acute or chronic
  - Energy or substance exchange

EC: Medical Device Directive

- The Medical Device Directive is a law that regulates the marketing of Medical Devices in the EC
- Soon to be substituted by an even stricter Regulation
- Details the device identification
  - Classification
  - Application (custom made, research, marketing…)
- Defines manufacturers responsibilities and duties
  - Essential Requirements for safety and performance
  - Surveillance
- Gives powers to the Local Authorities to control the placing on the market of the devices

Basic requirements in the MDD

- Give proof that the device is safe and effective for the intended use: **Technical File**
  - SAFE: testing as per standards
  - EFFECTIVE: non inferior to clinical state of the art (clinical trials)
- Give proof that the manufacturer can manufacture device **consistently**: Quality Management System
  - Controlled manufacturing
  - Lot/ serial number control
  - General management procedures for suppliers, maintenance, calibration
- **Continuous control**: vigilance and surveillance
  - Post market clinical trials

Risk based approach

Vulnerability of the human body

Potential risks associated with the devices

- Criteria
  - applied to a vast range of different medical devices and technologies
  - combined in various ways in order to determine classification
- Control
  - Higher for higher risk classes
  - From self- declaration to comprehensive device and company audit by Notified Body

Risk classes: criteria

- Intended use (central circulatory or nervous systems increase class)
- Duration of use (duration increases class)
- Kind of contact with the body (not invasive, invasive, implantable)
- Active or not active

Risk classes in EU

- Mass production
  - Class III
  - Class IIb
  - Class IIa
  - Class I
- Custom made
- Clinical trials/ experimental use

Classification and control

- Class I: self declaration of compliance by manufacturer
  - band aids, ready-made reading glasses, surgical masks and gloves
- Class IIa and IIb: preliminary and annual audit by Notified Body on Technical File and on Manufacturing
  - Haemodialysis lines and machines; ECG; ventilators; needles of syringes; scalpels; tracheal tubes; ultrasound fetal heart detectors
- Class III: preliminary and annual audit by Notified Body on Design file, Technical File and on Manufacturing
  - Bovine heart valves; deep brain stimulators for Parkinson; bone implants with antibiotic; Coronary drug eluting stent; cerebrospinal drains

Special classes

- Custom made: self declaration+ clinician prescription
  - Glasses; dentures; most orthoses
- Clinical investigation: special authorization by CA and EC
  - Devices not yet legally approved, innovative
- Compassionate use: special authorization by CA and EC

A common trend: risk control

- Devices can be marketed only after **extensive testing**
  - Bench testing
  - In vitro- in vivo testing
  - Clinical trials
- Medical devices companies shall maintain a **Quality Management System**
  - GMP
  - ISO 13485
- Devices must be evaluated over time (**follow up**)
  - by the manufacturers
  - by the competent authorities

Risk subjects

- Manufacturer shall evaluate impact of use of the device:
  - On patient
  - On intended user
  - On bystanders
  - On general environment
- Manufacturer shall evaluate effect of product impact in all life cycle, from manufacturing to disposal

Scope of the MDD: Device

- Devices on the market must be SAFE and EFFECTIVE
- SAFE: The risk-benefit ratio must be favorable for the patient (or end user)
  - Expected clinical benefit
  - Side effects
  - Residual risk
- EFFECTIVE: The device must effectively perform clinical actions
  - Intended use defines the expected clinical benefit
  - Clinical benefit must be proven by clinical data
- The patient and end user are always protected, even against continuous research

Scope of the MDD: QMS

- Quality of products must be consistent over time
  - Manufacturer responsibility
  - Control by Notified Body for higher classes
- Quality is the output of a complete management system
  - Design
  - Manufacturing
  - Control and product release
  - Connected activities: maintenance, training, environmental control and cleanliness, sterility

Medical Devices Technical File

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Technical documentation
Annex II of new Regulation

- Technical documentation
  - clear, organized, readily searchable and unequivocal way
- Prepared by the manufacturer
- Verified by the NB in case of high classes

1. DEVICE DESCRIPTION AND SPECIFICATION, INCLUDING VARIANTS AND ACCESSORIES

- Product name, code, unique identification number
- Intended use, population, principles of operation
- Risk class
- Explanation of novel features/ comparison to previous devices
- Accessories and parts
- Variants
- Device specs (see next slide)
- Similar devices

Device specifications

- key functional elements:
  - parts/components (including software if appropriate),
  - formulation or composition,
  - functionality
- raw materials
  - incorporated into key functional elements
  - contact with the human body (direct or indirect)
- technical specifications (features, dimensions and performance

2. INFORMATION SUPPLIED BY THE MANUFACTURER

- Complete set of labels and IFU
  - All packaging
  - including logistic containers in case of special transport conditions
- All translations

3. DESIGN AND MANUFACTURING INFORMATION

- Understanding the design stages
  - Input (product requirements) & output (product specifications)
  - Review
  - Verification and validation
  - Design change control
- Design and manufacturing location
  - At manufacturer
  - Subcontractors
  - Suppliers

4. RES for DESIGN AND MANUFACTURING INFORMATION

- List of essential requirements and applicable standards
- Complete information and specifications,
  - Product specs (drawings, composition, SW modules)
  - Raw material specs
  - Manufacturing processes and their validation,
    - adjuvants & residuals
  - Quality control
    - continuous monitoring
    - final product testing

5. RISK/BENEFIT ANALYSIS AND RISK MANAGEMENT

- Risk benefit analysis
- Risk control measures
- Results of risk control
  - Clinical evidence
- NOTE: EN ISO 14971:2012

6. PRODUCT VERIFICATION AND VALIDATION

- *All the* verification and validation testing
  - Rationale for no new testing (example: for biocompatibility)
- Their critical analysis
  - Statistical relevance
  - Applicable standards

6.1.a Pre-clinical data

- Engineering, laboratory, simulated use, animal tests
- Published literature applicable
  - Substantially equivalent device
- Manufacturer's testing
  - test design, complete test or study protocols,
  - methods of data analysis,
  - data summaries and test conclusions

6.1b Required preclinical data

- Biocompatibility ISO 10993
  - all materials in direct or indirect contact
- Physical, chemical profile ISO 10993
- Microbiological characterisation;
- Electrical safety and electromagnetic compatibility; IEC 60601
- Software verification and validation IEC 62304
- Stability/shelf life
- Performance and safety

6.1.c/d Clinical data

- Data regarding clinical performance and clinical benefit on human beings
  - From literature
  - From past data
  - From clinical trials
- Clinical trials are regulated to ensure maximum protection to the human beings

6.2. Additional information in specific cases

- Drug: file for safety, quality and usefulness
- Human and Animal origin: identification and risk profile (see RES 10)
- Absorbables: absorption studies, local tolerance, interaction with drugs, ISO 10993 toxicity
- Sterile: stetilization validation and cleanroom specs
- Measuring: accuracy proof
- Accessories/ combination: validation of combined use

Annex I: how it's made

- I General Requirements
- II REQUIREMENTS REGARDING DESIGN AND CONSTRUCTION
  - **Chemical, physical and biological properties**
  - **Infection and microbial contamination**
  - **Construction and environmental properties**
  - **Devices with a measuring function**
  - **Protection against radiation**
  - **Requirements for medical devices connected to or equipped with an energy source**
  - **Information supplied by the manufacturer**

General comments

- "**Designed and manufactured**"
  - Design criteria
  - Product specifications
  - Production control activities
- "**Minimize the risk**"
  - Evaluation of causes and of probability of risk
  - Control methods
  - Perfection is "impossible" but it is required to implement all possible solutions

RES 2 on risk

- Preferred order of RES:
  - Safe design and construction
  - Protection from uneliminable risk,
  - Information for safety (safe use description) and training
- Information on residual risk SHALL be provided

RES 7 on design

- Impact of processes on material properties
- Mechanical, surface, chemical properties and specs
  - Including (nano) materials released into the body (RES 7.6)
- *Compatibility between the materials and substances used and biological tissues, cells, and body fluids taking account of the intended purpose of the device and absorption, distribution, metabolism and excretion*

RES 8 on infection and contamination

- Design to
  - allow handling, cleaning, sterilization
  - Reduce exposure to contamination, prevent contamination
  - Easy performance of cleaning and resterilization
  - Clear user indication of sterile state

RES 18: layperson

- Layperson skills
  - Taking into account the variations in technique and environment
- Easy information and any need of training
- Procedure for
  - Testing the functioning of the device
  - Warning of device malfunction

What is a technical standard?

- Provide requirements, specifications, guidelines or characteristics
  - Test methods
  - Acceptance criteria
- Can be used **consistently** to ensure that materials, products, processes and services are fit for their purpose
- ISO has published more than 21k standards
- Other bodies include IEC, ASTM

Some standards in our everyday life

- ISO 8601 date and time format
- ISO 3166 country codes
- ISO 9001 Quality management system

- ISO 7304 Alimentary pasta
  - -2 assessing cooking
- ISO/TC 133 Clothing size system

Standards in the medical industry

- Device lifecycle is regulated as per:
  - ISO 13485 for Quality Systems
  - ISO 14971 for Risk Management
  - ISO 14155 and various guidelines for Clinical Investigations
- Each product category is then regulated by technical norms
  - For electro medical devices
  - For sterile devices
  - For devices in contact with the body
  - Multiple harmonised and not harmonised norms for technical regulation

Medical Devices Quality Management System

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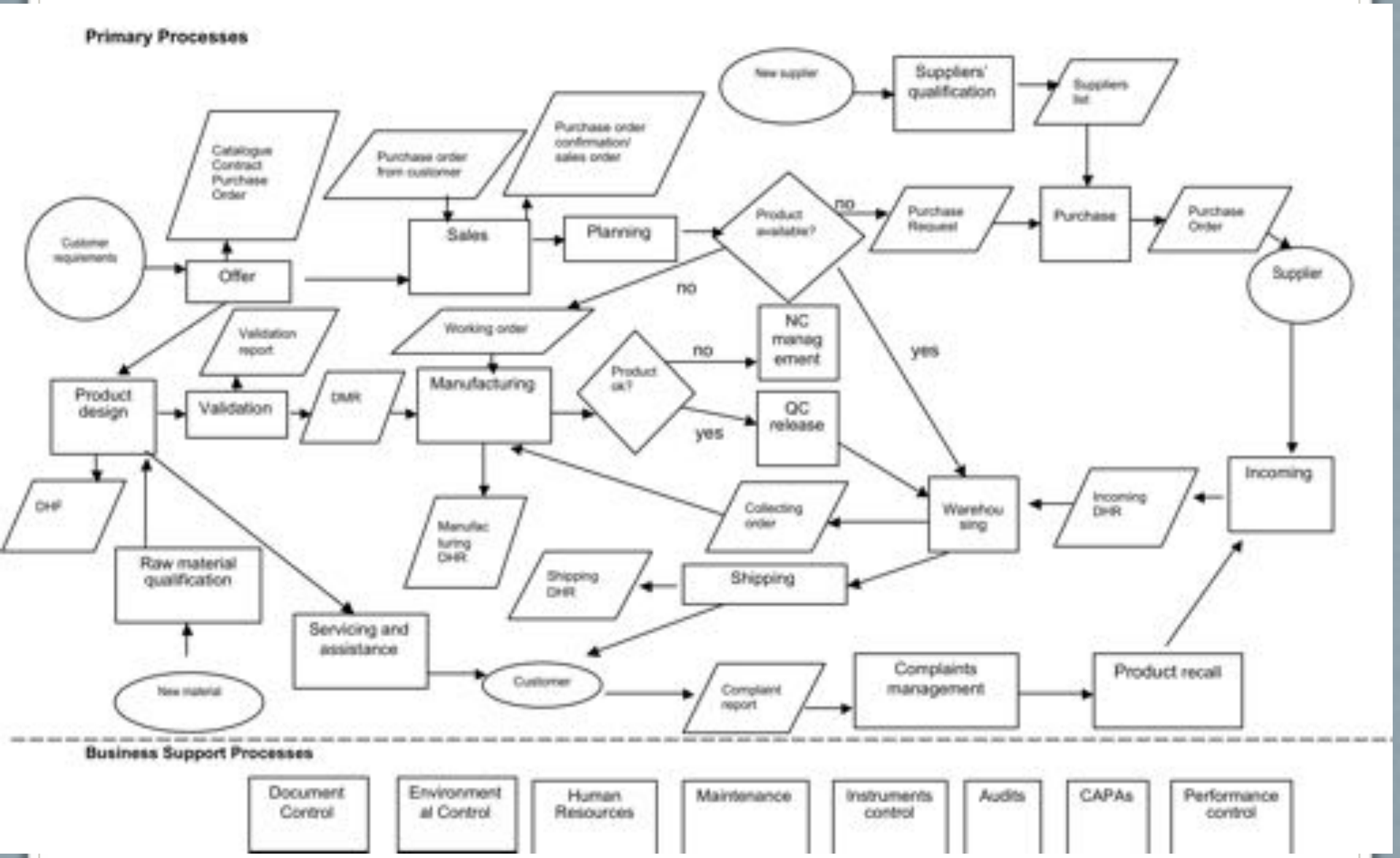
Manufacturers obligations

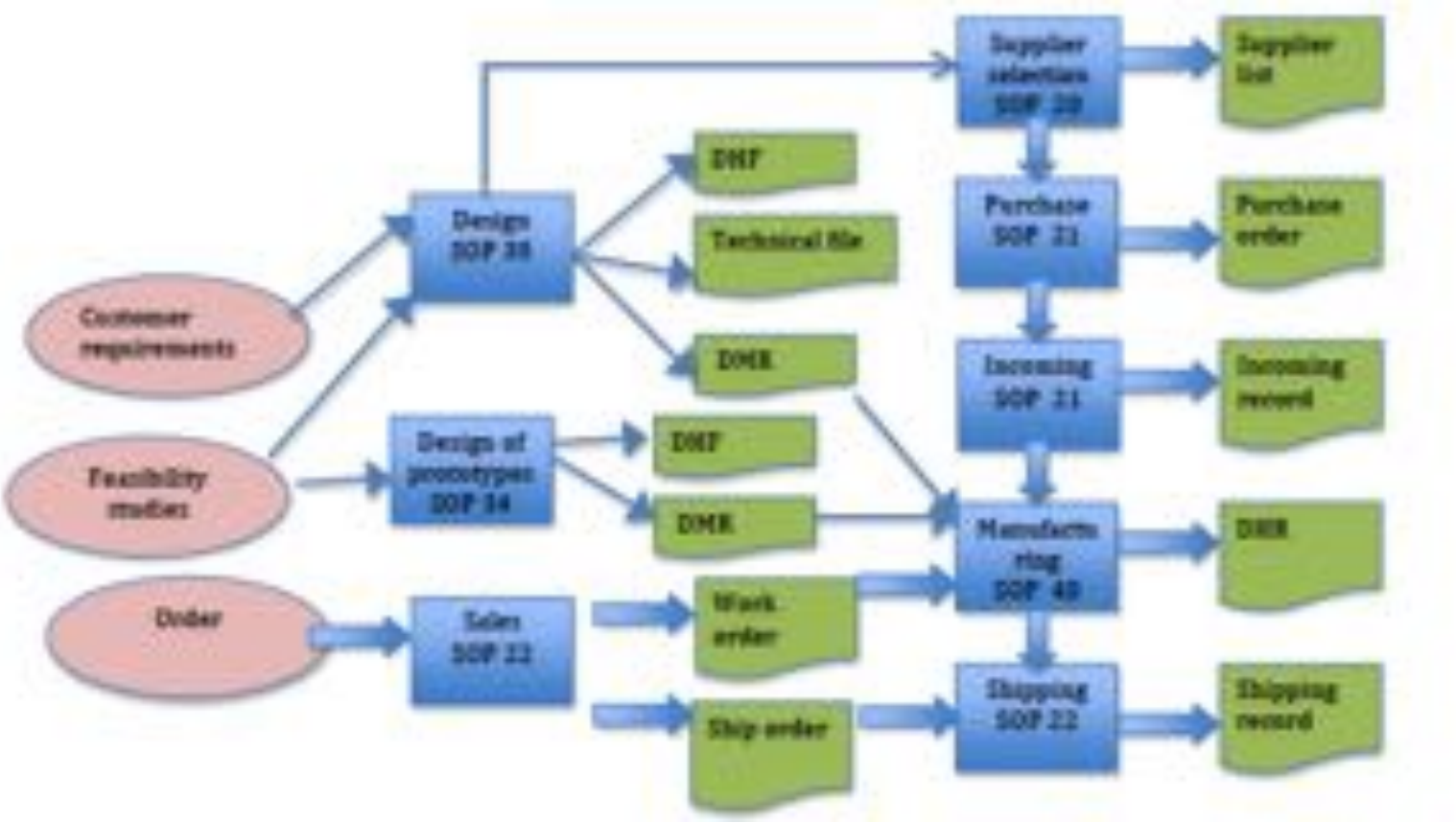
- Design control
- Product and process validation
- Clinical evaluation
- Manufacturing as per Good Manufacturing Practice guidelines
- Retention of records
- Continuous surveillance
- Device database
- Strict control on Post Market information and follow up clinical trials

Device life cycle

Typical processes for any company

- Quality Management/ Management review
- Training
- Design and Development
- Production Management
- Service Provision
- Logistic Management
- Customer Relationship Management
- Product Purchasing/ Supplier qualification


Primary Processes
New supplier
Suppliers' qualification
Suppliers list
Catalogue Contract Purchase Order
Purchase order from customer
Purchase order confirmation/ sales order
Customer requirements
Offer
Sales
Planning
Product available?
no
Purchase Request
Purchase
Purchase Order
Supplier
no
Working order
NC manag ement
yes
Validation report
Product design
Validation
DMR
Manufacturing
Product ok?
no
QC release
yes
Incoming
DHF
Manufac turing DHR
Collecting order
Warehou sing
Incoming DHR
Raw material qualification
Shipping DHR
Shipping
Servicing and assistance
New material
Customer
Complaint report
Complaints management
Product recall
Business Support Processes
Document Control
Environment al Control
Human Resources
Maintenance
Instruments control
Audits
CAPAs
Performance control


Customer requirements
Feasibility studies
Order
Design SOP 38
Design of prototypes SOP 34
Sales SOP 22
DHF
Technical file
DMR
DHF
DMR
Work order
Ship order
Supplier selection SOP 20
Purchase SOP 21
Incoming SOP 21
Manufacturing SOP 40
Shipping SOP 22
Supplier list
Purchase order
Incoming record
DHR
Shipping record

Quality standard for design
ISO 13485 clause 7

- Clinical and safety requirements: user needs
  - Expected benefit
  - Mechanism of action
- Device technical development
  - Tech drawings
  - Composition
  - SW modules
- Device technical verification and validation
  - Bench test
  - Safety test on animal models (ISO 10993)
  - Design transfer from prototype to industrial scale

Standard for risk management
ISO 14971

- Search of potential harmful events or device malfunctions
- Evaluation of probability and of impact on patient health (severity)
- Search of risk control measures (example: safe design, protections and alarms)
- Evaluation of risk-benefit ratio

Standard for biocompatibility
ISO 10093

- Assessment of device impact on human body in terms of risk of bio-incompatibility
- Device identification: materials, manufacturing methods, sterility level
- Evaluation of available information
- Planning of test to collect new information
  - Material characterization
  - In vitro
  - In vivo

Manufacturing quality EU GMP ISO 13485

- The device shall be manufactured consistently to the Device Dossier
  - Equivalent to the prototype
  - Constant level of quality
  - Full traceability
- Standard operation procedures for Company management
  - Industrial processes
  - Equipment
  - Personnel

Standard for clinical trials
ISO 14155

- Clinical trials on humans: authorized by Ethics Committee
  - Device with favorable risk- benefit ratio for each participant
  - Good statistical significance
- Difficult study design
  - Placebo? Mock device?
  - Number of participants
  - Data from animal models

Any questions, guys?