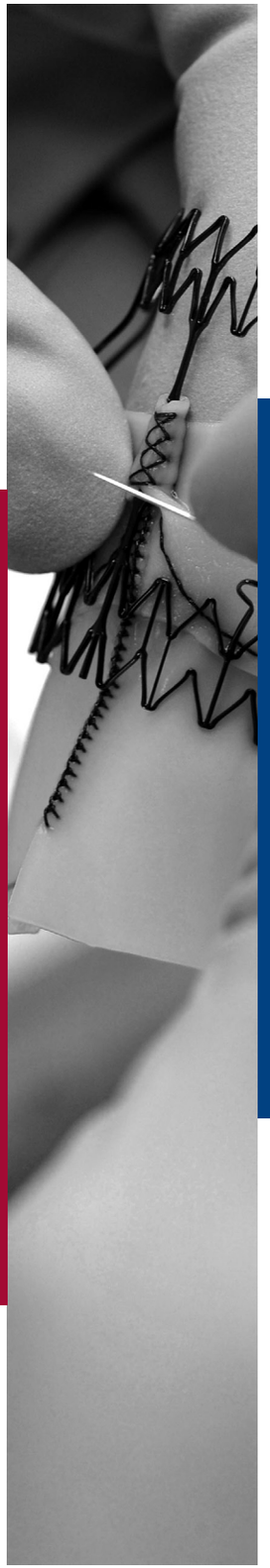
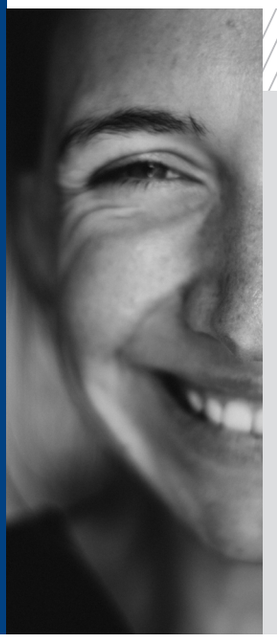
CORCYM

WE TAKE LIFE TO HEART





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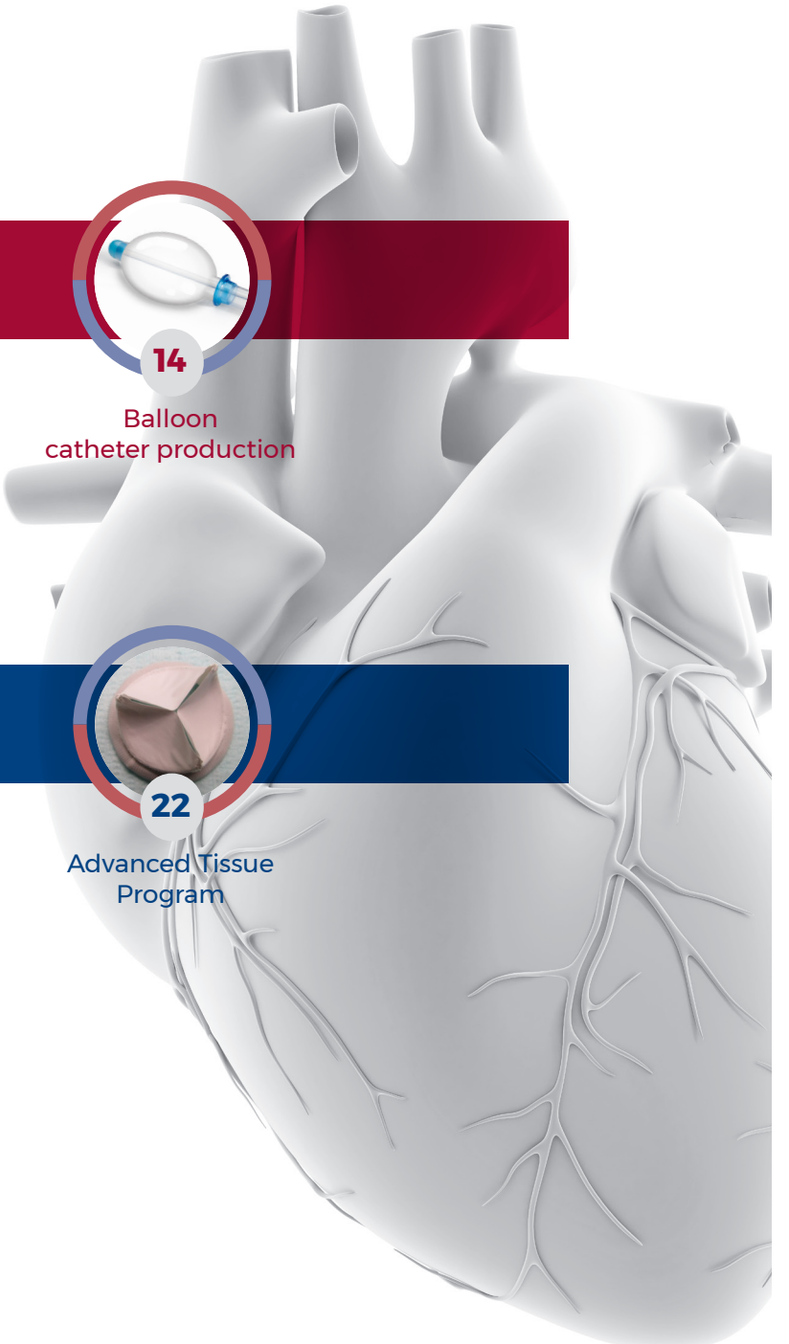

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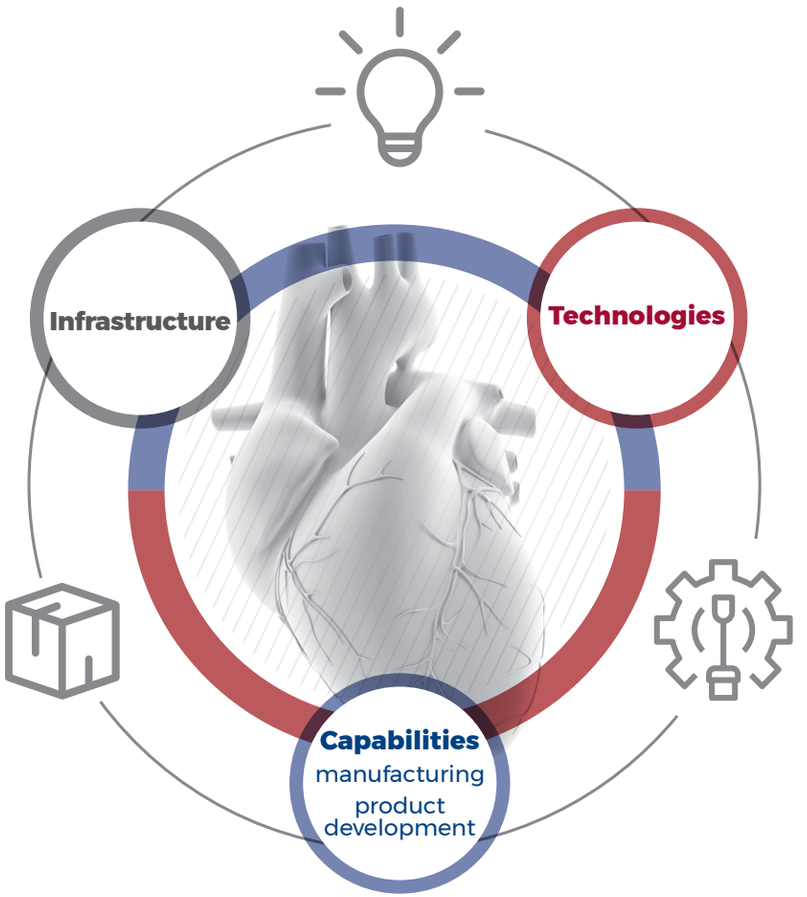
Quality controls

CORCYM

WE TAKE LIFE TO HEART

As a fully integrated medical device company with decades of experience in researching, developing and producing high-quality implantable devices, we have developed a set of distinctive technologies, capabilities, and infrastructure.

>60 years of history

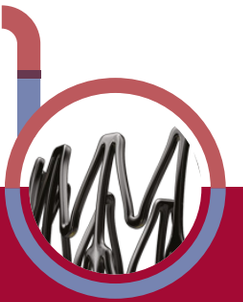


SALUGGIA

VANCOUVER

From **Saluggia** to **Vancouver**, through the introduction of new products for our own portfolio, we have developed expertise in design transfer for industrialization and ramp up of production.

CORCYM
technologies



Carbofilm coating

Carbofilm is a thin pure carbon film used as a coating suitable to almost all types of material and surfaces, to maximize biocompatibility of implantable devices.

Pyrolitic carbon coating

Pyrolytic carbon is an amorphous carbon allotrope ideal for application in implantable devices, due to its high strength, chemical inertness and wear resistance.

3

Nitinol machining

Nitinol is a metal alloy of nickel and titanium with unique properties, including super elasticity and “shape memory”.

4

Pericardium processing

Over 40 years of experience in the manufacturing of biological valves components from bovine pericardium.

5

Balloon catheter production

In-house production of the baloon catheter.

Carbofilm coating

Carbofilm is a thin pure carbon film used as a coating for materials of biomedical interest. The coating has physical and biological properties substantially similar to those of bulk isotropic pyrolytic carbon and since 1985 our plant manufactures implantable devices which incorporate components and materials coated with Carbofilm.

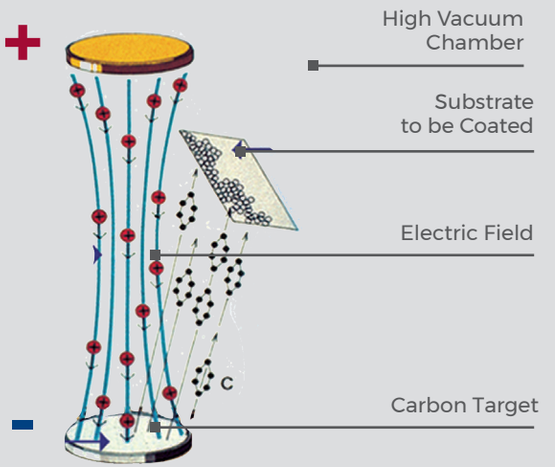
The Carbofilm process is based on a patented low temperature Physical Vapour Deposition (PVD) technology which does not involve chemical reactions and the related heat generation, thus allowing the coating of temperature sensitive substrates as polymers and metals.

The thickness of **carbofilm layer is 0.5 µm** (1000 times thinner than Pyrolytic Carbon).

The Carbofilm technology allows the application **to almost all types of material** and to very complex-shaped components.

P.V.D.= Physical Vapour Deposition

- No chemical reaction
- Room Temperature
- Thickness: 0.5 µm

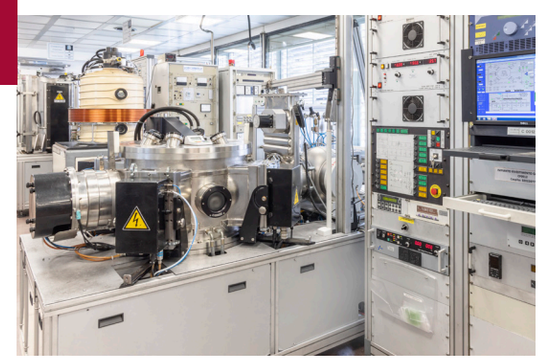


MAJOR BENEFIT:

The Carbofilm coating favours hemocompatibility, minimizing the risk for pannus formation and favouring a gentle tissue ingrowth.

EQUIPMENT:

The Carbofilm coating process is currently leveraging on 7 specialized equipment working in a ISO8 clean room to coat Nitinol stent, titanium components, fabric, surgical thread and OEM products.



Carbofilm treatment coating consists of 3 steps:

- Erosion of surface of the component to be coated, to prepare it for Carbofilm™ deposition
- Stellite alloy thin substrate deposition
- Carbon thin substrate deposition

Quality controls include:

- Thickness control
- Adhesion control
- Visual inspection
- Overall dimensional control

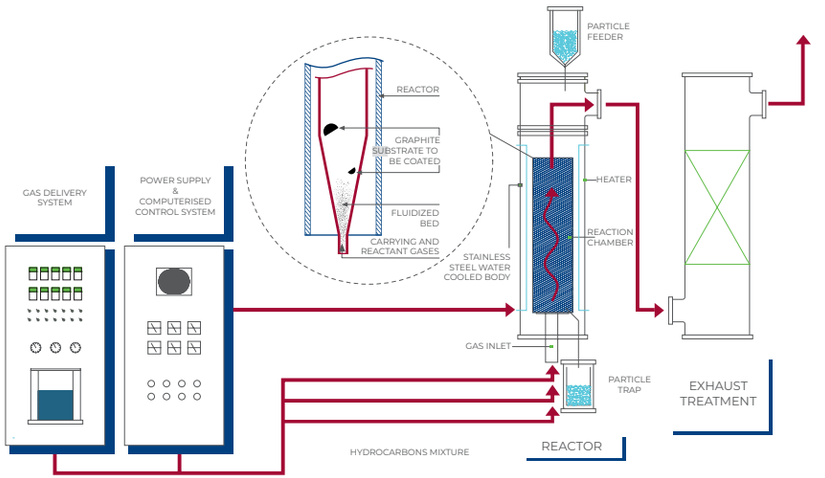
2

Pyrolitic carbon coating

Pyrolytic carbon is an an amorphous carbon allotrope, deposited onto graphite substrates with a Chemical Vapour Deposition processes.

The Pyrolytic Carbon coating consists of Silicon Carbide crystallites dispersed in a turbostratic Carbon matrix, between the diamond and the graphite structure.

Pyrolytic Carbon Technology



- **The coating is obtained by means of a Chemical Vapour Deposition (CVD) process** involving the pyrolysis of hydrocarbons at temperature higher than 1000° C in a fluidized bed reactor
- The reactant gases are diluted with Argon, which acts as an inert carrier
- During the coating the graphite substrates are continuously levitated, following a convection-like motion, in a fluidized bed, consisting of a large number of refractory ceramic beads. This prevents the graphite substrates from prolonged contact with the reaction chamber walls, that would result in uneven coating
- The fluidized bed also acts to make the coating conditions more uniform and stable
- **The thickness of Pyrolytic Carbon deposited is about 0,5 mm**

MAJOR BENEFIT:

The Pyrolytic Carbon is the **material of choice for different medical prostheses** due to its:

- Chemical inertness
- High strength
- Hardness
- Wear resistance
- Fatigue resistance

EQUIPMENT:

The Pyrolytic Carbon coating process is currently leveraging on different areas, with a total of 16 coaters.

3 Nitinol machining

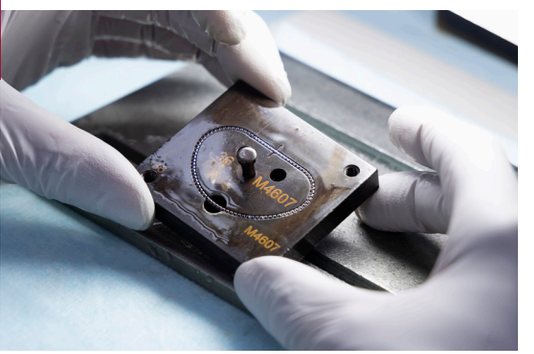
Nitinol is a metal alloy of nickel and titanium with unique properties, including super elasticity and “shape memory” properties.

The **Nitinol components** (Perceval stent and Memo Core) are obtained with a series of subsequent manufacturing steps which starts from laser cutting of a blank tube, continues with a number of surface finishing and thermal setting operations, and finishes with Carbofilm coating:

- Laser cut
- Deburring and shot peening
- Thermal setting
- Electropolishing
- Quality controls: visual inspection, dimensional inspection, transition temperature verification and Dye Penetrant inspection
- Carbofilm coating

The **main equipments** used in the stent manufacture are:

- Laser cutting system
- Deburring equipment
- Shot peening machine
- Shape setting tools
- Laser welding
- Thermal setting furnace
- Electrochemical polishing equipment
- Carbofilm holders
- Carbofilm coaters
- Quality Control equipments



Pericardium processing

The tissue valve is produced from two sheets of **bovine pericardium,** suitably treated and shaped via processes perfected by Corcym for the production of stented and stentless bioprostheses that cumulated over decades years of clinical experience.

The manufacturing process consists of a series of chemical treatments of the pericardium tissue and assembly operations (in general by sewing) to create the final tissue components.

The **pericardium tissue processing steps** include the following (mostly performed in in ISO6/ISO8 clean rooms):

- Tissue harvest at the slaughterhouse
- Raw pericardial tissue receiving
- Raw pericardial tissue processing and inspection (visual inspection, gross-cleaning, prefixation,...)
- Sewing according to a specific pattern
- Glutaraldehyde Fixation and Leaflets Formation
- Quality controls: visual inspection, Functional inspection
- Sterilization
- Aseptic Processing
- Packaging and Sterility Batch Release

Balloon catheter production

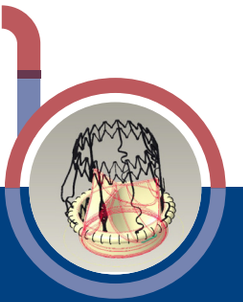
Balloon catheter is indicated for in-situ dilation of the valve after implantation.

The production and assembly of the Post-dilation Catheter accessory is in-house, in an ISO 8 clean room:

- Batching and Balloon blow thermoforming with a dedicated equipment and molds
- Batching and Catheter components assembly:
  1. *Balloon Proximal sealing, with welding of the balloon with extruded tube*
  2. *Heat setting of subassemblies with inner rod to stabilize dimensions*
  3. *Distal end wire assembly*
  4. *Fixation of the Luer lock with the extruded blue tube by gluing*
- Balloon involvement and insertion in PTFE tube piece to protect the balloon
- Printing of the size on Luer connector
- Leak test on 100% of units at balloon inflating pressure at 4 bar
- Visual & dimensional controls on 100% finished catheters

CORCYM

new product development

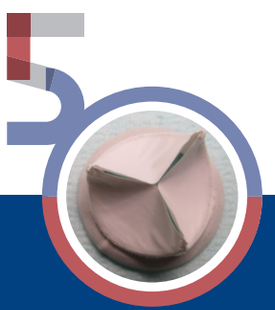


New product design

Device testing

Clinical trial design and execution

Regulatory Affairs



Advanced Tissue Program

New product design

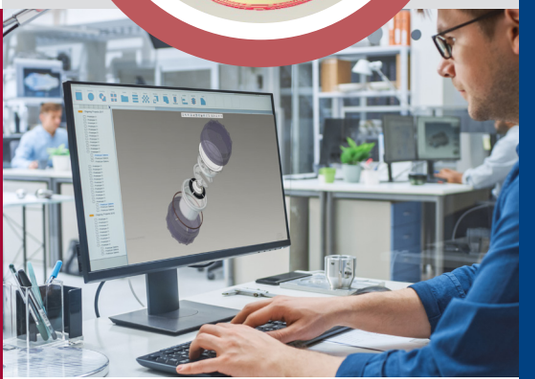
Corcym Product Design team averages about 20 years of medical device design & development experience.

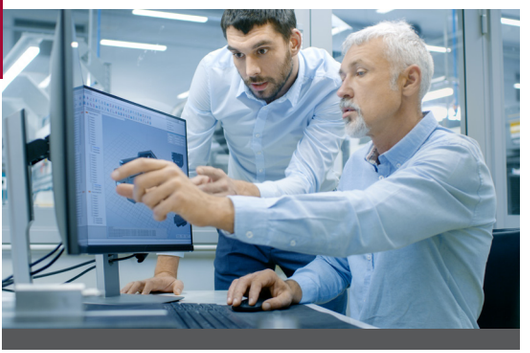
The combination of our culture, creativity, and engineering synergies allow to get efficient and timely results.

Corcym Product Design team provides technical expertise for new device development or improvement of existing devices.

Our capabilities:

- Design and development of implantable devices and related accessories
- Virtual device modelling (finite element analysis for structural simulation; device-fluid interaction)
- Sample prototyping through components 3D printing, fabrication, and device assembly
- Bench testing including simulation of implant procedure





2 Device testing

An effective medical device verification and validation is critical to guarantee a smooth FDA/CE approval. Our medical device verification and validation services for Class I, II, and III devices are carried out by our dedicated team of medical device testing experts and can effectively support throughout the Development Process, till the submission and the market release.

Hydrodynamic and durability valve assessment

- Measure the key indicators of the valve performance: pressure gradients, Effective Orifice Area (EOA) and Regurgitant Fraction % (RF%), under pulsatile and steady flow conditions
- Accelerated Wear Testing (AWT) and Dynamic Failure Mode (DFM) to assess the valve durability and to identify the potential failures modes
- Customized testing mockups, chambers and fixtures, rigid or compliant

Material properties assessment

- Stress-strain curves on materials, including biological materials; stent radial force measurement
- Material fatigue testing.
- Scanning Electron Microscope (SEM), spectroscopy, metallography, and optical inspection

Analysis and computational modeling (FEA)

- Static and dynamic structural analysis

3

Clinical trial design and execution

Clinical studies are an essential step to ensure that the medical devices are safe and effective, and they fulfill their intended use. The Corcym's Clinical Affairs team provides clinical expertise and strategy services for pre- and post-marketing clinical data collection for medical devices.

Our team of experts has decades of experience in providing guidance to collect the proper clinical evidence, design the relevant clinical activities, and conduct clinical studies on medical devices to meet the local regulatory requirements.

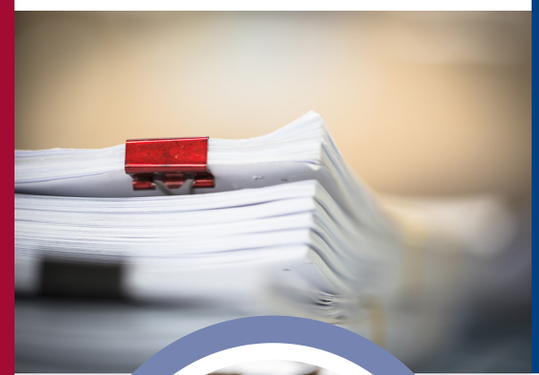
How can we help:

- Provide support on compliance to ISO 14155, by setting-up quality procedures and reviewing the clinical activities
- Design and develop clinical study protocols appropriate to the device development stage (pre- or post-market; exploratory, confirmatory, observational; FIH, feasibility, pivotal, registry, etc.)
- Support on the Clinical Trial Management and Monitoring
- Develop Post-Market Clinical Follow-up Studies (PMCF) to identify potential residual risks of approved devices, collect data and gain clarity regarding the long-term clinical performance of the products

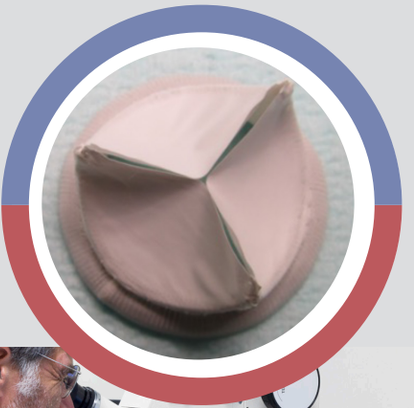
Regulatory Affairs

Before a Medical Device is sold, the manufacturer must obtain the local Competent Authority or the Notified Body's approval by presenting the evidence that the device is safe and effective for its intended use.

Our medical device regulatory experts, who gained a deep experience in the European and International regulatory field with hundreds of successful submissions, can support throughout the entire product development life cycle, to meet the local regulatory requirements.



Advanced Tissue Program



Corcym has a team of experts dedicated to the research and development of advanced materials for medical devices.

Our capabilities:

- Advanced treatment for pericardial tissue to:
  - *improve tissue durability and prevent mineralization*
  - *allow aldehyde-free solution or dry storage*
  - *optimize morphological and mechanical properties*
- Use of polymeric or composite materials for medical devices
- Use of tissue engineering materials for medical devices

CORCYM
manufacturing

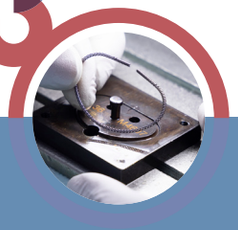
1

Device Processing and Assembly

2

Machining of all implantable-grade materials

3



Laser cutting, welding, marking

4

Chemical laboratory

5

Microbiological laboratory

Device Processing and Assembly

Corcym is a fully integrated design, manufacturing, and distribution company with decades of experience with long term implantable devices.

Our team is highly skilled at development of processes, validation of test methods, installation of equipment, process validation and processing of semi-finished and finished implantable products.

We leverage operator driven process improvements to guide development of processes, tooling, and templates to gain efficiency and reduce ergonomic challenges associated with manual assembly techniques.

Corcym's own products bring together mechanical, synthetic, and biological components and our engineers work closely with manufacturing to develop and implement manufacturing processes. Quality process controls are established and monitored for trends to identify opportunities for further improvement.

Our solution preparation laboratories can produce chemical formulations to support manufacturing (working solutions), chemically treat biological materials, sterilize products, and provide long term storage. Chemical specifications are confirmed in house using a variety of methods including pH testing, osmolality, density,
and UV-Visible Spectrophotometry.

Corcym's microbiology laboratory works with our designers to develop sterilization methods and perform process validations.
The lab also provides full testing capabilities to support medical device manufacturing, including bioburden, sterility testing for product release and endotoxin (LAL) testing.

Our supply chain supports the entire process from vendor selection, raw material procurement through receiving inspection and warehousing on the front end to finished good storage and shipment to customers.

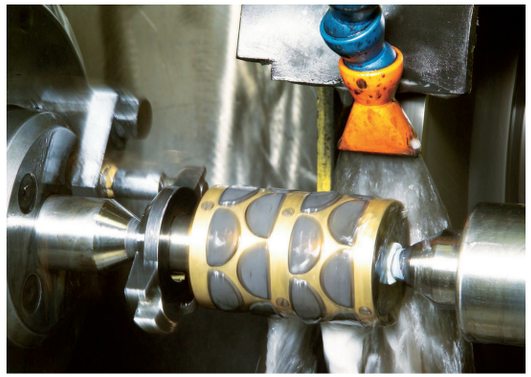
2

Machining of implantable-grade materials

(Titanium, Nitinol, Pyrocarbon, among many other specialty metals, plastics and alloys)

The main specialized equipment used to machine implantable-grade materials (accuracy up to ± 3 µm) **are:**

- EDM (Electric Discharge Machines)
- Grinding machine (surface finishes of pyrocarbon components)
- Facing machine (turning machine that can machine both ends of a piece of bar/piece stock simultaneously)
- Milling machines manufacture of parts from titanium / graphite bars for milling and turning



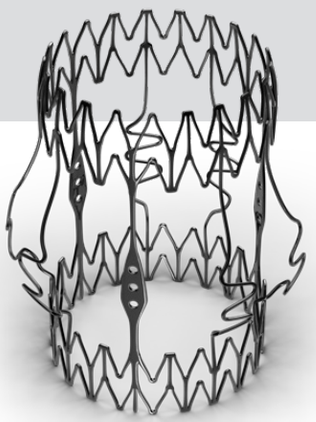
3

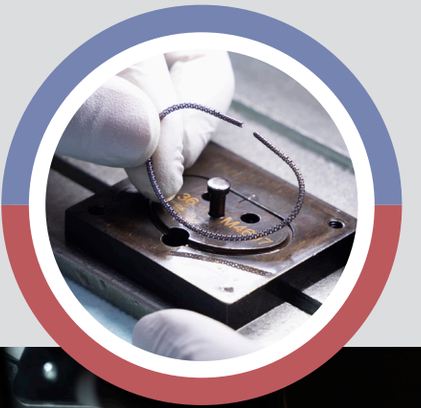
Laser cutting, welding, marking

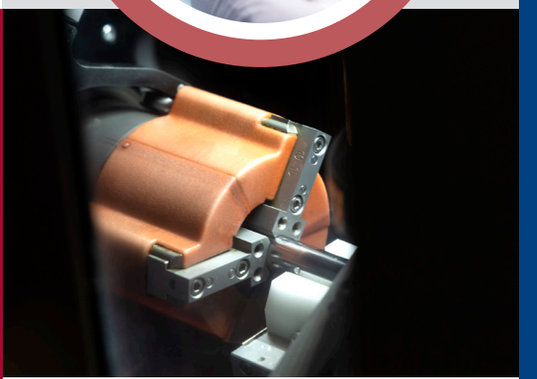
(Yag, CO_2)

Different technologies for different uses:

- **Cutting**: High quality cutting with centesimal precision (even in round shapes) for high-speed processing applications
- **Welding**: High quality welding on micro parts in Nitinol
- **Marking**: The laser marker based on Fiber Laser Technology, specifically dedicated to industrial Direct Part Marking (DPM) applications







Chemical laboratory

Gas chromatography for analysis of ethylene oxide residues and for analysis of ethylene hydrochloride

Qualitative analysis: Identification of substances present in aqueous and non-aqueous extracts, by absorption at specific wavelengths. Applied to silicone analysis and chemical toxicity of the finished product

Air permeability analysis of papers and Tyvek (finished product packaging)

pH analysis for biological analysis on finished product, pH analysis on auxiliary production solvents

5 Microbiological laboratory

Microbiology Services (Saluggia and Vancouver)

- Corcym Laboratories offer full microbiology testing services, performing validated routine and investigational testing for bioburden, endotoxin (pyrogens), sterility testing (liquid/device direct transfer), biological indicators and cleanroom environmental monitoring (particles/microbial)
- Microbiology team has expert knowledge of ISO standard compliant validation and routine control of sterilization processes - liquid chemical, steam, ethylene oxide, vaporous hydrogen peroxide (VHP), filtration, irradiation (gamma), and also aseptic processing (isolator based)

Laboratory analysis:

- Bioburden test and validation methods (ISO-11737-1)
- LAL Test (GEL CLOT) and validation method (USP and AMMI/ANSI ST72)
- Sterility test and validation method (USP and ISO-11737-2)
- Sterility test of biological indicators (USP)
- Bacterial load identification (USP)

Environmental Controls

- Microbiological controls of air and surfaces (ISO 14644 series)
- Particle controls (ISO 14644 series)

Validation of sterilization processes:

- Steam Sterilization (ISO 17665-1)
- Sterilization with ethylene oxide (ISO 11135)
- Chemical sterilization (ISO 14160)
- Aseptic mediafilla (ISO 13408-1)


PYREX
500ml
Made in Germany
250
200
150
100

CORCYM

Infrastructure

Prototyping lab

Clean Rooms

3

Custom equipment tooling

4

Sterilization

5

Quality controls

Prototyping lab

Corcym can provide multiple prototyping technologies for proof-of-concept evaluation.

Our engineering team can support you through the entire prototyping process of cardiovascular implantable devices.

Our capabilities:

- Nitinol components laser cutting, deburring, thermosetting and electropolishing
- 3D rapid prototyping
- Pericardial valves: raw material harvesting and selection, pericardial tissue laser cut, and chemical treatment
- Tissue valve assembly, leaflet shaping and final sterilization

2 Clean Rooms

Corcym manufactures implantable devices in controlled environments ranging from **ISO Class 8 to ISO Class 6** and incorporating Isolators for aseptic processing.

The total area of the cleanrooms is 1200 m^2 (13000 ft^2) in Saluggia and 850 m^2 (9200 ft^2) in Vancouver. **Cleanrooms are classified per ISO 14644-1**.

Cleanrooms are kept within specification for temperature, humidity, and pressure, ensuring particulate and bioburden are controlled. Corcym's Microbiology Laboratories carry out cleanroom monitoring including airborne particles, airborne microbials and surface microbial.

Trained operators follow good cleanroom practices for gowning and activities performed within the rooms themselves.

Routine cleaning ensures ongoing cleanliness of the rooms while maintenance ensures functionality of the HEPA filtration systems, calibration of flow benches and biological safety cabinets.

Pass throughs are utilized to transfer materials into and between cleanrooms, maintaining product cleanliness during manufacture.

3 Custom equipment tooling

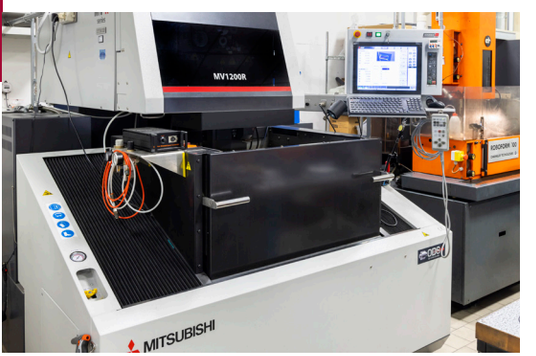
The tooling shop is in charge of supporting manufacturing, creating custom fixtures and tools with high precision execution.

All machines are equipped with 3R or Erowa holding system, to ensure the maximum repeatability and accuracy.
Turning, grinding and milling machines ensure the preparation of electrodes or directly the preparation of the parts.
Below a description of the most distinctive machines:

Wire cut EDM Mitsubishi model MV1200R
- High precision execution => ±0.005mm
- Worktable 600x300x150mm
- 5 axes
- 3R system for a wide range of holding and cut execution
- Different type of wire materials
- Minimum radius R 0.15mm

RAM EDM CHARMILLES model FORM E350
- High precision execution => ±0.005mm
- Worktable 350x250x250mm
- 4 axes in continuous, +1 axis free rotation
- EROWA system for a wide range of holding
- Different type of electrodes materials

3D PRINTER STRATASYS model OBJECT 30 PRIME
- Worktable 820x620x590mm
- Minimum layer 0.028mm
- Different type of plastic materials



Steam sterilization

- Five production steam sterilizers (autoclaves) are available for in-house steam sterilization (3 in Saluggia, 2 in Vancouver)
- Validation and routine control of the sterilization processes according to ISO 17665-1
- Terminal steam sterilization of finished medical devices.
- Steam sterilization of supplies for aseptic processing, including sterile barrier systems (containers/closures).
- Steam sterilization of supplies for general cleanroom use (tooling, fixtures, carboys etc.).

Quality controls

No industry faces a higher mandate for quality than medical device manufacturing. Our quality system offers a complete oversight of the production process – from material sourcing to product delivery - and each individual device undergoes functional testing, dimensional and visual inspection before release, leveraging on the most advanced technologies:

Metallographic analysis

- Laboratory for the preparation of samples to be tested in resin: lapping, truncation and polishing of the samples.
- Metallographic analysis - SEM (Scanning Electron Microscopy)
- Micro hardness measurement

Dye penetrant inspection

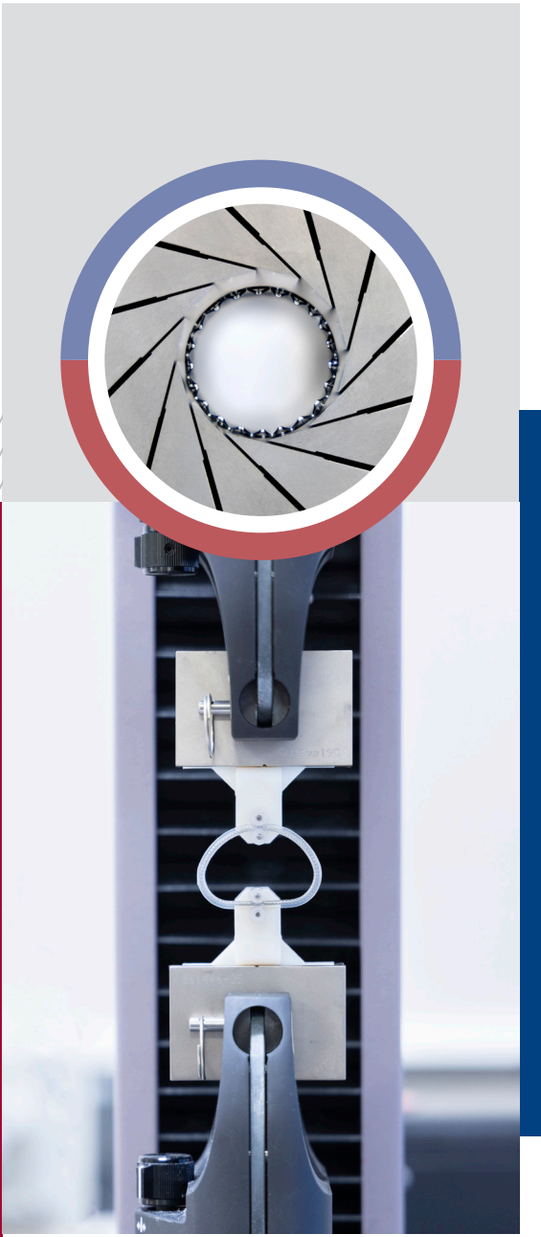
- Samples preparation and automatic cleaning
- Dye penetrant application, excess removal and application of developer
- Inspection analysis in the dark room
- Post cleaning

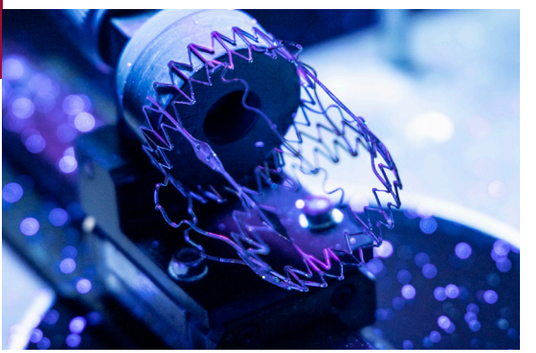
Metrological laboratory

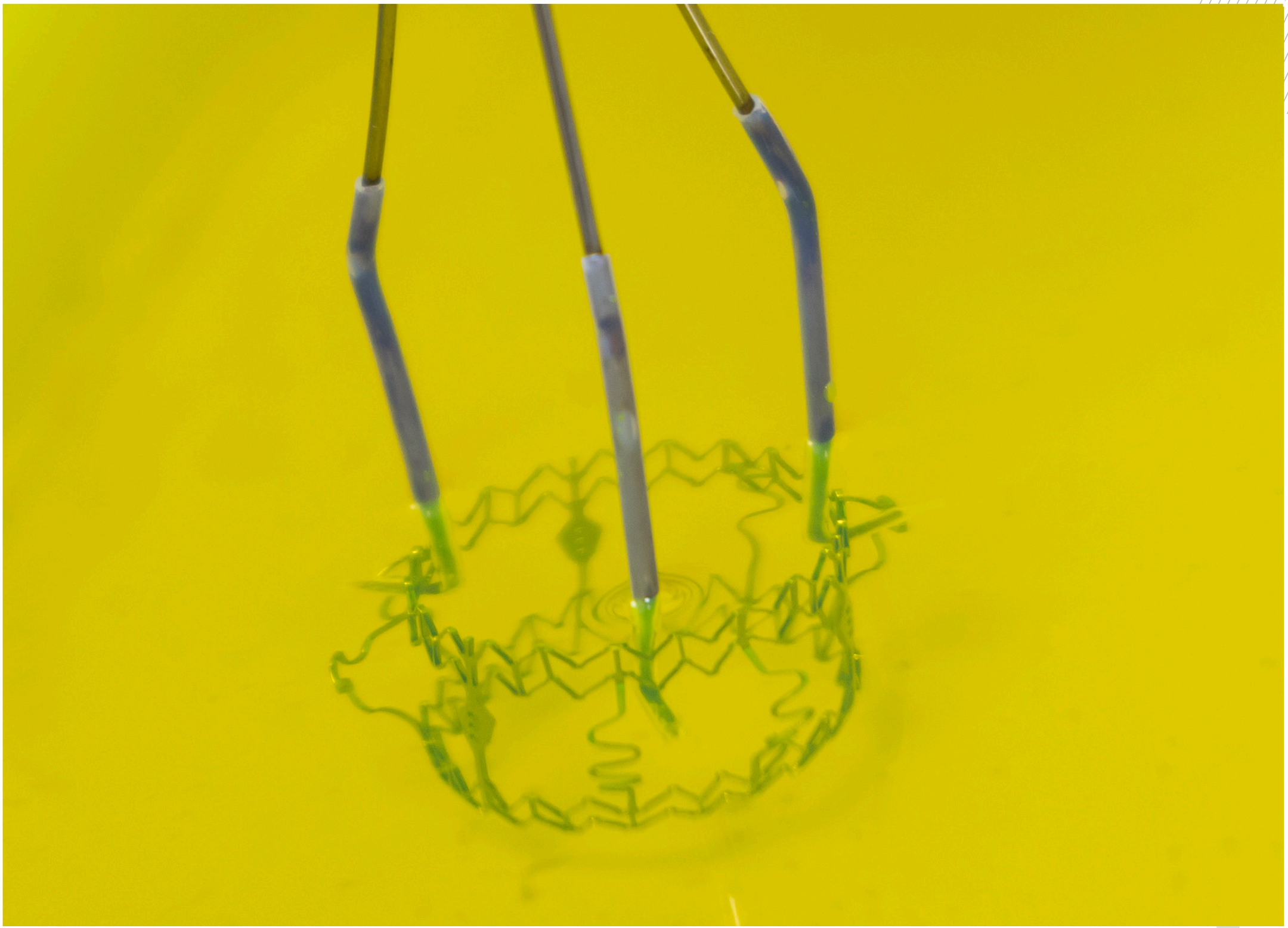
- Ultra-High Accuracy CMM
- OGP
- Custom equipment for 100% functional tests

Digital X-Ray inspection machine

- Sensor with 76 µm pixel pitch to produces high resolution digital images
- Magnification from x1 to x4 within the effective imaging area of 233 x 291 mm







CORCYM SALUGGIA FACILITY
MAIN CERTIFICATIONS

ISO 45001 Occupational Health and Safety Management System

International Organization for Standardization ISO 13485

Environmental Management System ISO 14001

Good Manufacturing Practice GMP Certified

CE

QMS Manufacturing Site Brazil

QMS Manufacturing Site South Korea

MDSAP Medical Device Single Audit Program

Proficient in Class I and II medical devices

QSD Manufacturing Site Taiwan

FDA 21 CFR Part 820

KPMG Manufacturing Site South Korea

ISO 9000 Quality Management System

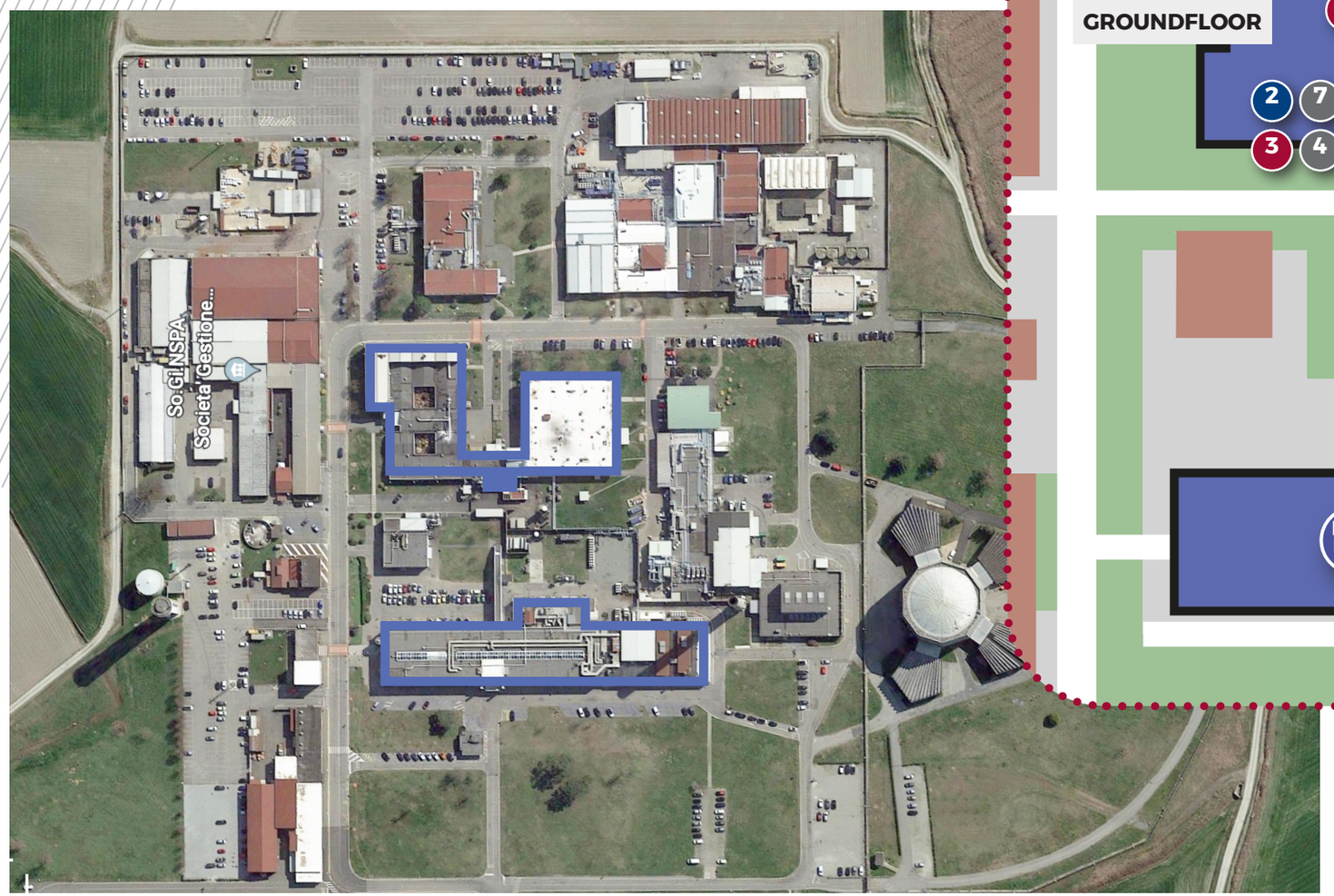
QMS Manufacturing Site Taiwan

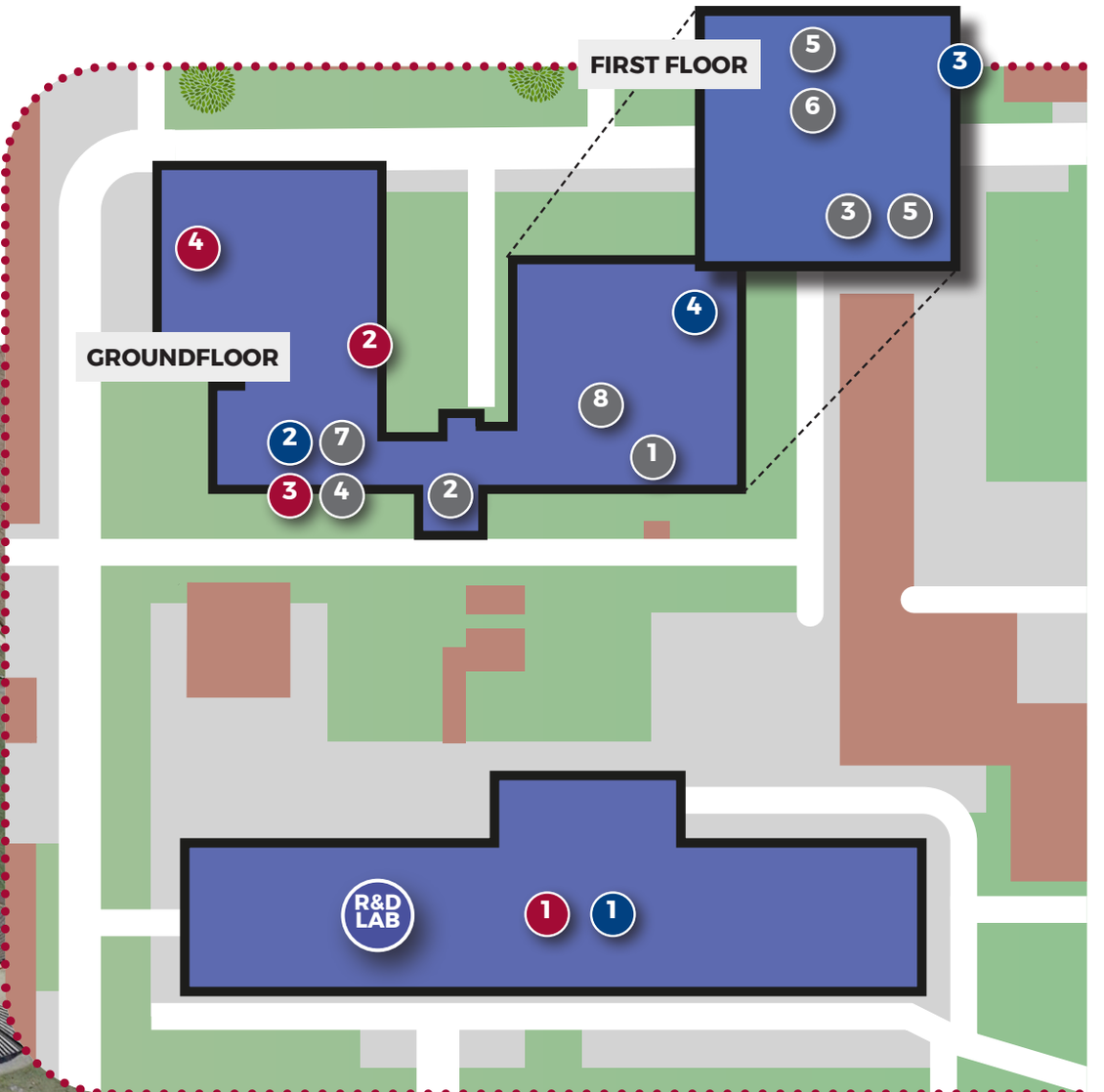
SALUGGIA
CORCYM CAMPUS

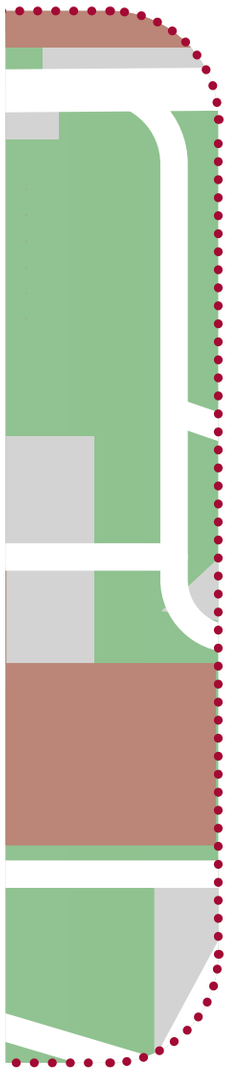
Total focus and dedication to our Customers
the Cardiac Surgeon and their Patients

Renewed investment and commitment
to provide solutions to fight structural heart disease

An agile and flexible company
that can rapidly decide and adapt to a changing world







PERCEVAL

1. **STENT MANUFACTURING (Nitinol)**
   Nitinol is a metal alloy of nickel and titanium with unique properties, including superelasticity and shape memory.
2. **STENT QUALITY CONTROL**
   All stents are inspected to check their dimensions and integrity.
3. **CARBOFILM COATING**
   Carbofilm is a thin pure carbon film used as a coating suitable to almost all types of materials and surfaces, to maximize biocompatibility of implantable devices.
4. **PERICARDIUM**
   The tissue component is produced from two sheets of bovine pericardium, suitably treated and shaped. The manufacturing process consists of:
   - BOVINE PERICARDIAL TISSUE SELECTION
   - TISSUE PRE-FIXATION
   - TISSUE SEWING & STENT ASSEMBLY
   - QUALITY INSPECTION
   - TISSUE TREATMENT

MECHANICAL HEART VALVES

1. **COMPONENTS MANUFACTURING**
   All components are manufactured and prepared for the following steps.
2. **PYROLITIC CARBON COATING**
   Pyrolytic carbon is an amorphous carbon allotrope ideal for application in implantable devices, due to its high strength, chemical inertness and wear resistance.
3. **MACHINING**
   The main equipments normally used to machine implantable-grade materials are Electric Discharge (EDM), grinding, facing and milling machines.
4. **CARBOFILM COATING (FOR CUFFS AND BICARBON ORIFICE)**
   Carbofilm is a thin pure carbon film used as a coating suitable to almost all types of materials and surfaces, to maximize biocompatibility of implantable devices.
5. **QUALITY CONTROL**
   Quality control is based on an extensive battery of in-process inspections and tests to ensure conformance with established control parameters and specifications.
6. **MATCHING**
   The assembly process includes selecting and inserting matching leaflets into housings with matching internal hinge recess dimensions.
7. **SEWING**
   Sewing cuffs are manufactured inside a room with controlled environment, using tooling and templates depending on the valve models.
8. **ASSEMBLY & STERILIZATION**
   The valves are mounted onto the holder and the finished valves are inspected, packaged, sterilized and released for distribution.

MEMO

1. **CORE MANUFACTURING (Nitinol)**
   Nitinol is a metal alloy of nickel and titanium with unique properties, including super elasticity and shape memory. Laser cutting technology aloows unique core flexibility.
2. **MOULDING**
   The Nitinol core is embedded into the silicone sheath.
3. **CUFF AND RECHORD SYSTEM SEWING**
   Memo Platform has Carbofilm coated cuff. Memo 3D ReChord and Memo 4D feature ReChord System to standardize neochordae implantation.
4. **ASSEMBLY & STERILIZATION**
   The rings are mounted onto the holder and then inspected, packaged, sterilized and released for distribution.

CORCYM VANCOUVER FACILITY
MAIN CERTIFICATIONS

International Organization for Standardization ISO 13485

ENVIRONMENTAL MANAGEMENT SYSTEM ISO 14001

GOOD MANUFACTURING PRACTICE GMP CERTIFIED

CE

QMS MANUFACTURING SITE BRAZIL

QMS MANUFACTURING SITE SOUTH KOREA

QMS MANUFACTURING SITE TAIWAN

MDSAP Medical Device Single Audit Program

Proficient in Class I and II medical devices

QSD MANUFACTURING SITE TAIWAN

FDA 21 CFR PART 820

KPMG MANUFACTURING SITE SOUTH KOREA

ISO 9000 Quality Management System

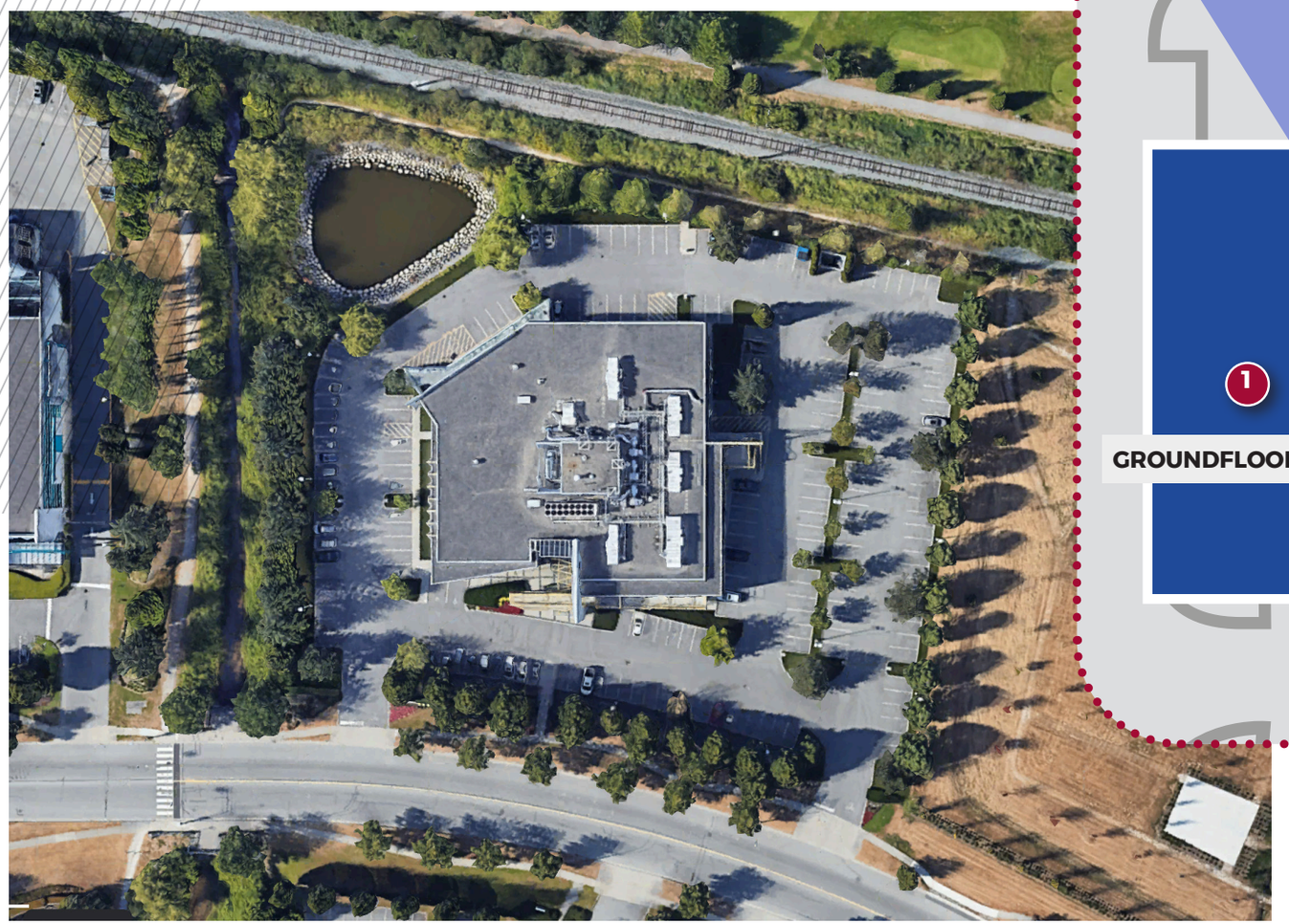

CORCYM

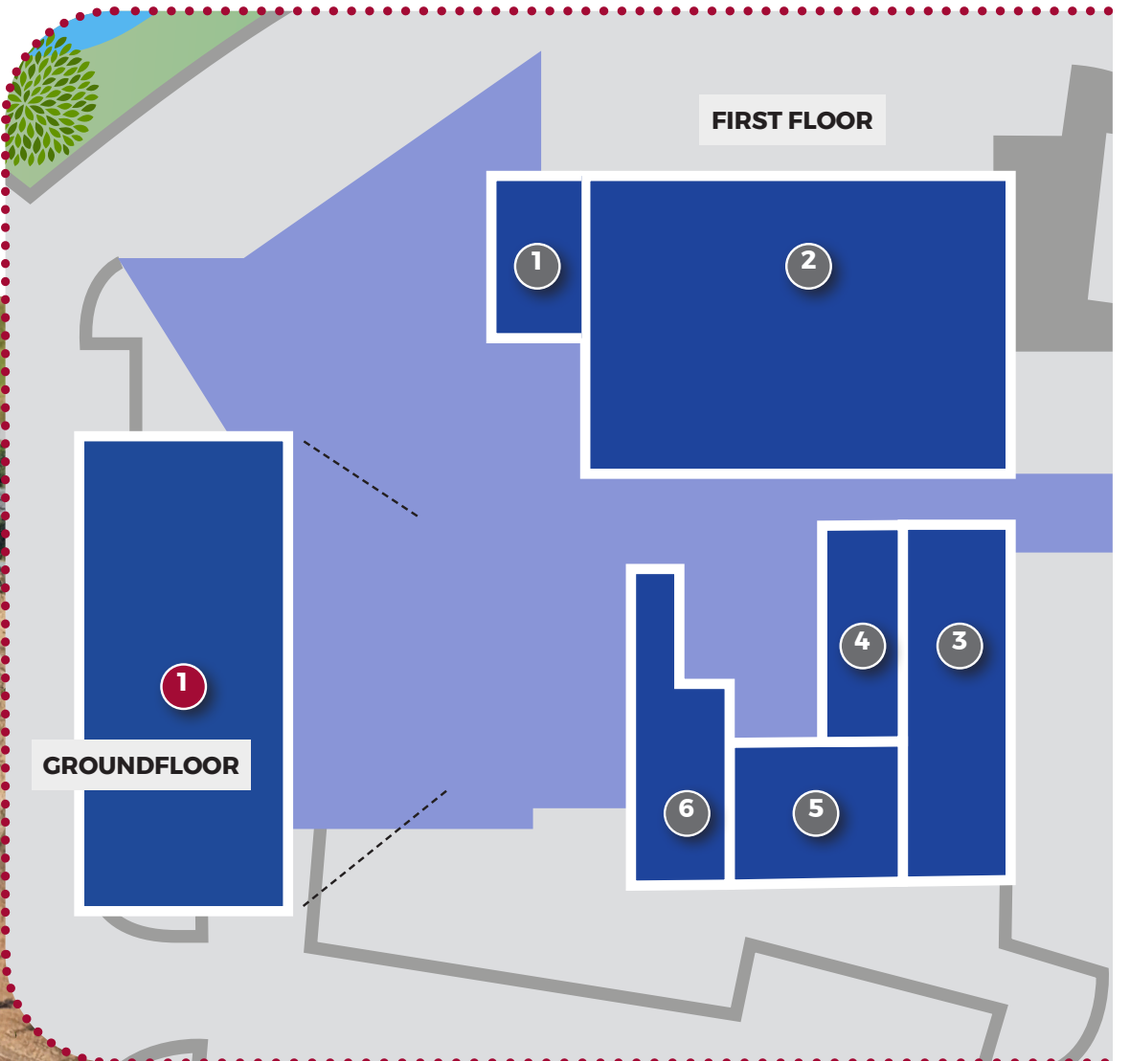
VANCOUVER CORCYM CAMPUS

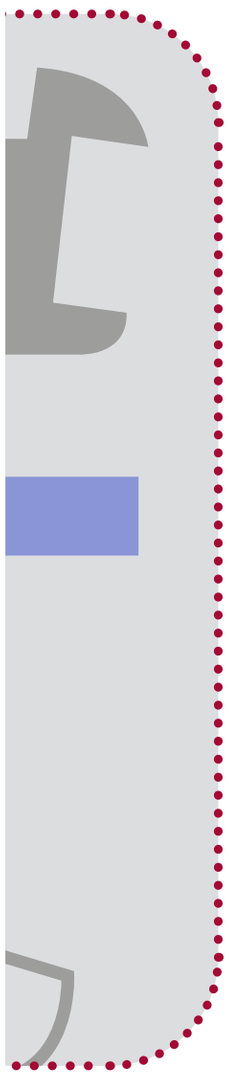
Total focus and dedication to our Customers
the Cardiac Surgeon and their Patients

Renewed investment and commitment
to provide solutions to fight structural heart disease

An agile and flexible company
that can rapidly decide and adapt to a changing world







GROUND FLOOR

1 **COMPONENT MANUFACTURING**
All components are manufactured and prepared for the following steps.

TISSUE PROCESSING
Incoming tissue is selected, cleaned, cut and prepared for further processing in the cleanroom.

FIRST FLOOR

1 **FINAL PACKAGING**
following sterilization and pending microbiology release, valves are packaged for their destination country based on the approved packaging configuration.

2 **TISSUE SEWING & SUBASSEMBLY**
alve subassemblies are produced from treated bovine pericardium and attached using sewing techniques to other components (eg fabric, stents, holders).

3 **QUALITY INSPECTION**
In process inspections and tests are performed to ensure conformance with established control parameters and specifications.

4 **SOLUTION PREPARATION**
In process inspections and tests are performed to ensure conformance with established control parameters and specifications.

5 **STERILIZATION**
liquid chemical sterilization is used to produce a sterile product, using aseptic processing where required.

6 **MICROBIOLOGY**
the laboratory performs all cleanroom monitoring as well as sterilization batch release for manufacturing.

CORCYM

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