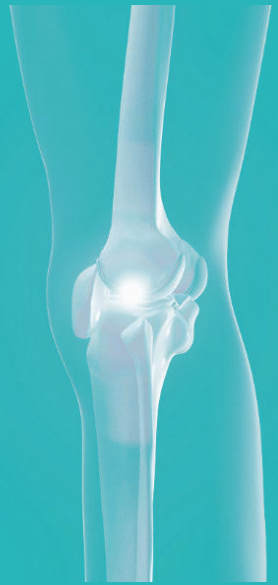
TRIP
Hemo-en biovigilantie

CO.DON
HUMAN CELL EXPERTS

16.11.2022

Cell based therapy for treatment of cartilage defects



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HUMAN CELL EXPERTS

Content

Cell therapy for cartilage defects

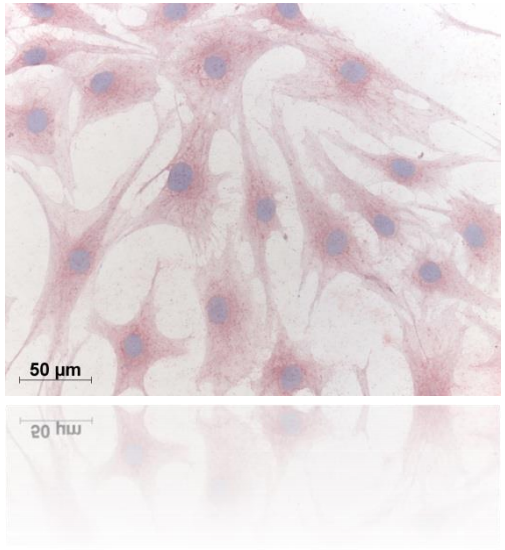
Short company history

Medical need

Procurement, processing and application

Product specifications, release tests

Reporting to TRIP



Foundation
CO.DON GmbH

1993

1997

2001
Public corporation
CO.DON AG

2004
co.don chondrosphere

Product development

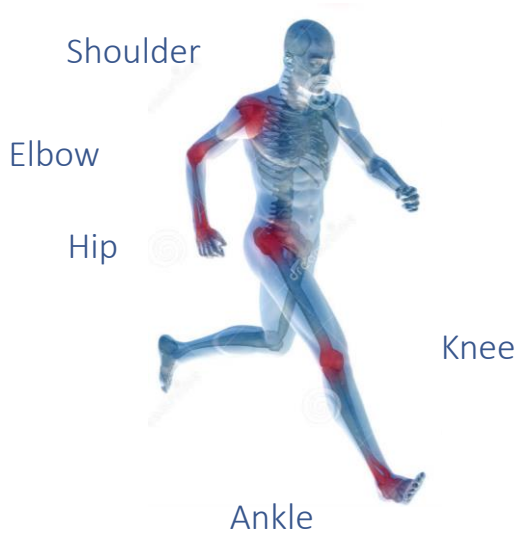
Licence for manufacturing
cell based therapies

2017
European MA (EMA)
Spherox

2018
Swissmedic MA

European expansion
sales Spherox

2021
Expansion production
site Leipzig

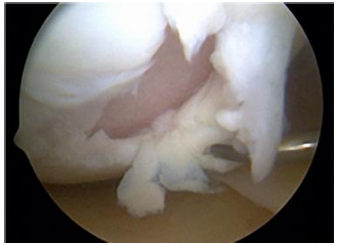


Cell-based therapies for treatment of hyaline cartilage defects

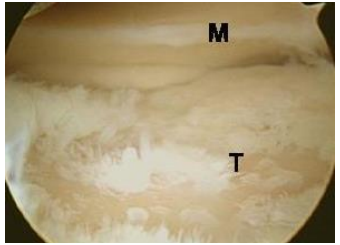
progression over time

Healthy cartilage

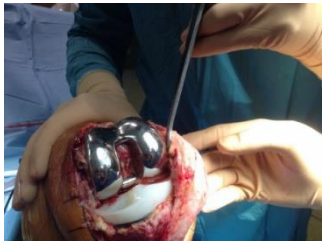
Symptomatic defect



Late stage osteoarthritis



Total joint replacement



Treatment time window

Autologous chondrocyte implantation

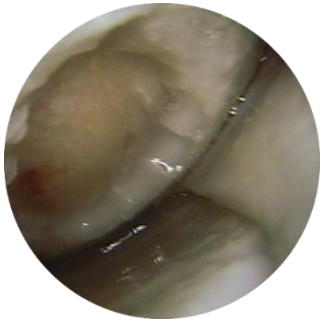
Spheroid based, tissue-engineered product

- Non-cellular based therapies (physiotherapy, hyaluronic acid, e.g.), mosaicplasty, microfracture, e.g.
- ACI development throughout the years
  - Monolayer cell-suspension (first generation ACI)
  - Monolayer cells in exogenous matrix: M-ACI (Vericel, TETEC)
  - Monolayer cells transferred in 3D cell culture to form spheroids (CO.DON AG)

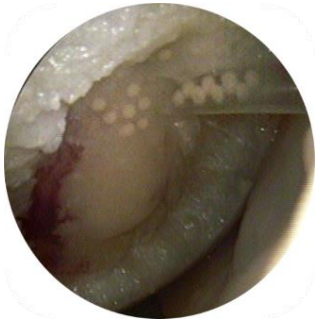
- ATMP: Advanced therapy medicinal product
- TEP, tissue-engineered product
- Donor = recipient: autologous

Clinical application of chondrocyte spheroids

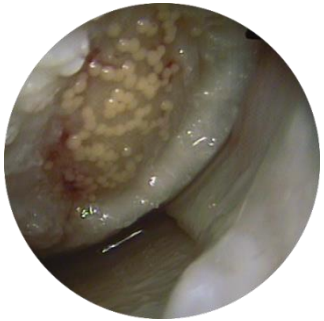
Autologous chondrocyte implantation



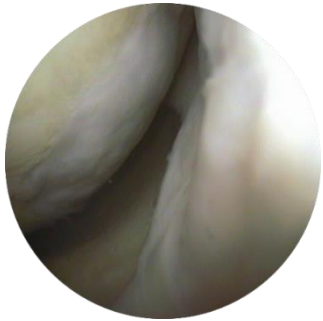
Cartilage lesion



Application by arthroscopy



Chondrocyte spheroids adhere to the defect



Follow-up 13 months after treatment

Chondrocyte spheroids

Product characteristics

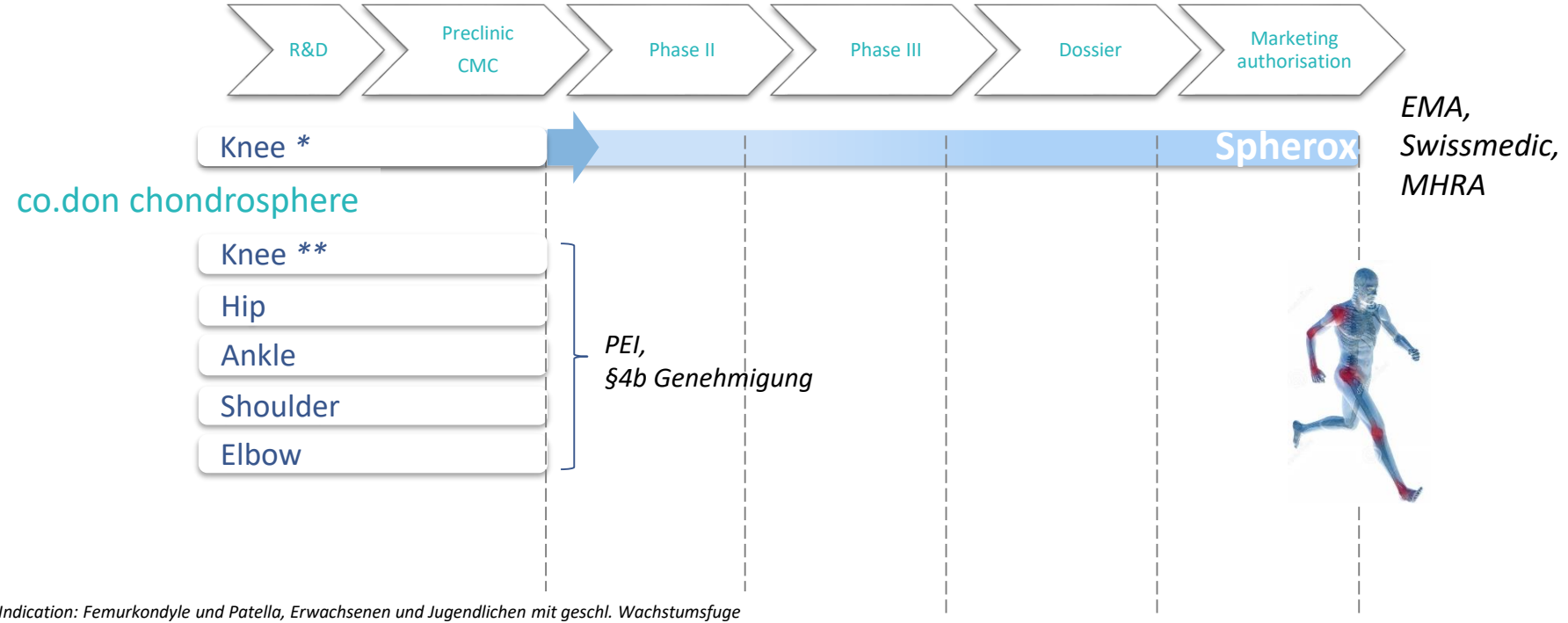
3D Cell aggregates
Embedded in ECM
ECM characteristic for cartilage
Synthesised by chondrocytes

Restored expression of chondrogenic genes
Phenotypic and Genetic stable cells
Tumorigenicity, biodistribution

Self-adhesive
Dose: 10-70 spheroids/cm2 defect

Product portfolio

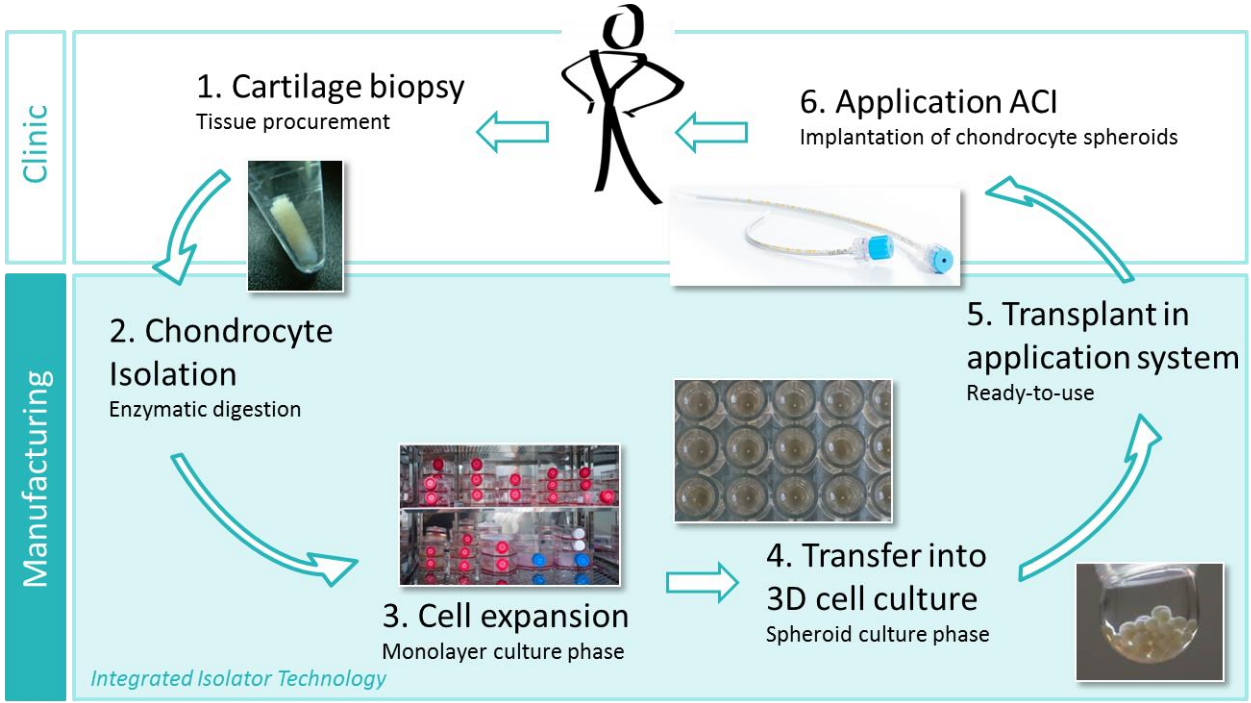
Pipeline



** Indication: Femurkondyle und Patella, Erwachsenen und Jugendlichen mit geschl. Wachstumsfuge*
*** Indication: Tibia, Erwachsenen und Jugendlichen mit geschl. Wachstumsfuge*

Manufacturing process

Procurement – processing - application



Manufacturing Process

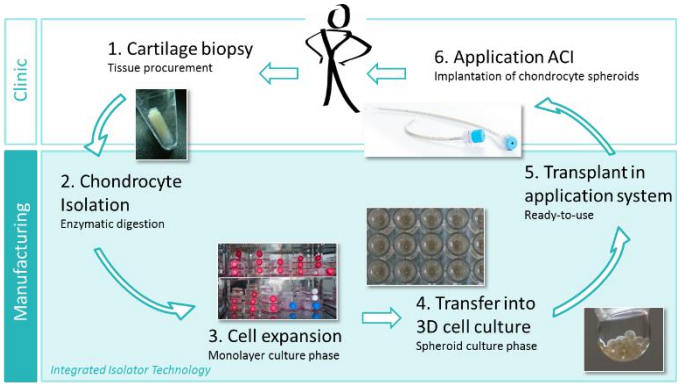
Integrated Isolator Technology IIT®

- fully integrated technology of the manufacturing process, clean room class A
- A-septic environment: continuous process chain from raw material to cell transplant
- Safety: extremely low risk of contamination

Manufacturing process

high level of reproducibility of products with the intended biological activity

- ATMP: Advanced therapy medicinal product
  - TEP, tissue-engineered product
- Donor = recipient: autologous
  - high variability between donors/products



- <u>Major challenges during CMC development</u>
  - Critical process parameter (cPP)
  - Critical quality attributes (cQA)
  - Robust manufacturing process

➢ Clinically relevant limits for operational ranges and release parameter

Product development

Safety and efficacy of the product

MA EMA/Swissmedic/MHRA

Safety

- Biodistribution, Tumorgenesis in small animal models
- Genetic & phenotypic stability
- QC Microbiological tests

Efficacy, proof-of-principle

- Large animal models, scheep, minipig

CMC development/ GMP processes

- Optimize manufacturing process
- QC Release Tests

Clinical trials Spherox

- Phase II + III: Proof of clinical efficacy and safety

Quality control regime

Safety and efficacy

Manufacturing process

Critical process parameters:

- Cell cultivation times/ efficacy
- Cell expansion/ genetic stable cells

In-process controls (>50)

- Cell number
- Cell viability
- Surface integrity
- Colour

Product Specifications

Critical Quality Attributes:

are chemical, physical, biological and microbiological attributes that can be defined, measured, and continually monitored to ensure final product outputs remain within acceptable quality limits

- Safety: microbiological tests (Eu. Ph.)
- Identity
- (Im)purity
- Potency

sterility
endotoxin
mycoplasm

Chondrocyte spheroids

Product specifications – safety first

critical quality attributes

Parameter	Method
Sterility	Test according Ph. Eur. 2.6.27 or Ph. Eur 2.6.1
Endotoxin	Test according Ph. Eur. 2.6.14
Mycoplasma	Mycoplasma test According Ph. Eur. 2.6.7
Identity	Biomarker mRNA levels (T/R) determined by qPCR
Purity	percentage synoviocytes as determined by Biomarker mRNA expression levels using qPCR
Potency	Biomarker mRNA levels (T/R) determined by qPCR
Allocation of the product to the patient	visual
Appearance of the product	visual
Cells/ spheroid	Cell count
Cell viability	Staining
Sterility	Test according Ph. Eur. 2.6.27 or Ph. Eur 2.6.1

Product-specific adjustments/validations established at CO.DON

Product-specific tests developed by CO.DON

Clinical validation of cQAs and cPP

Purity

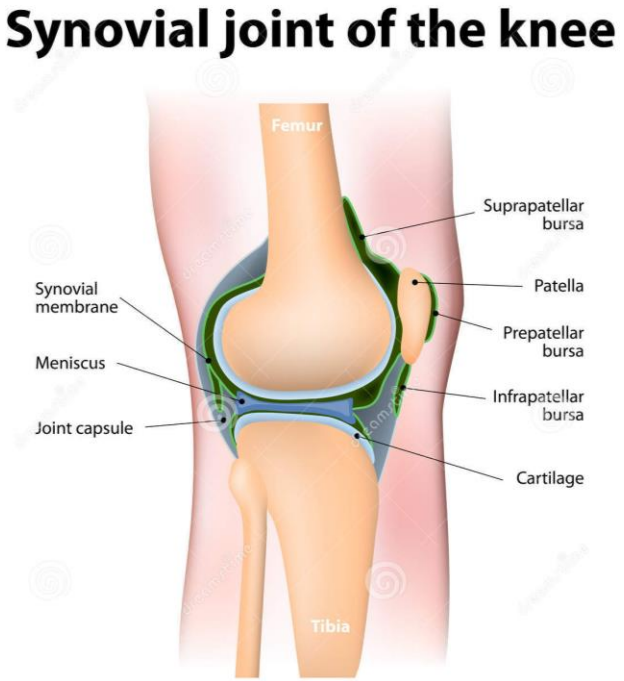
Potency

Purity test for Spherox

Synoviocyte-content in final product

- Risk of cellular contamination during biopsy procurement
- Synoviocytes
- *EBF3* mRNA levels representing % of synoviocytes in the product
- Basis for QC release test

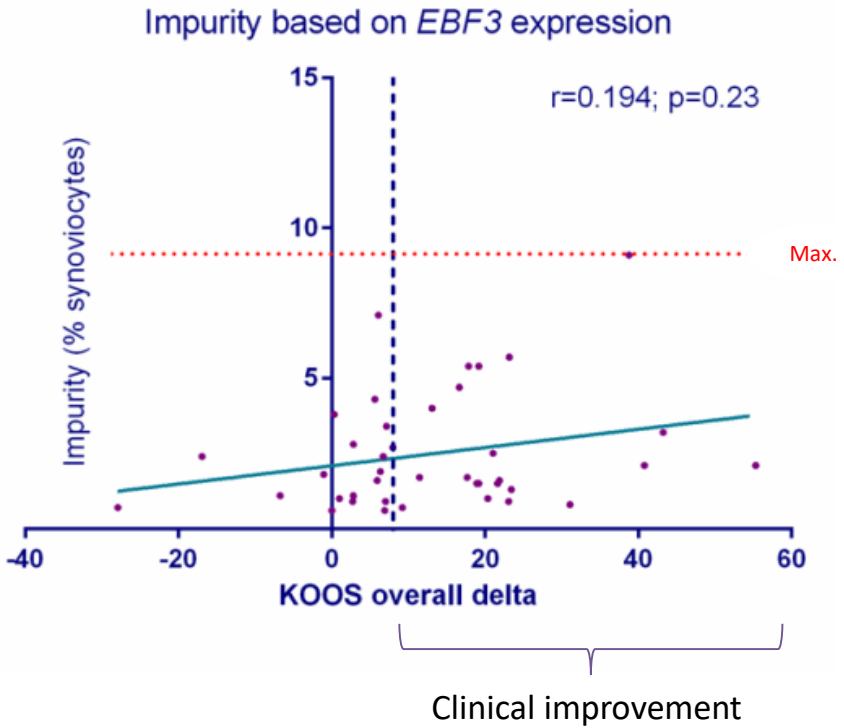
- Acceptance limit clinically validated



Release test for ‚Purity‘

Clinical validation

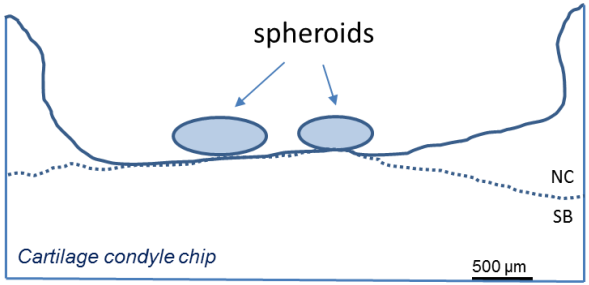
- Assessment of spheroids used in Phase II+III clinical trials
- No correlation with clinical improvement
- Limit justified by highest contamination with clinical improvement

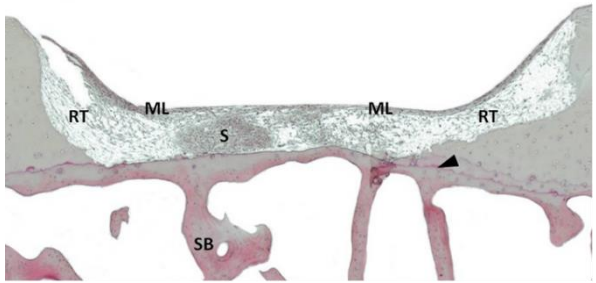


Release test for ‚Potency‘

Potency assay

- Human cartilage repair model
  - Proof of biological activity of the final product
  - Not eligable for release test
  - Find a biomarker that correlates with regenaration capacity of the product?
  - Development of a surrogate potency assay
  - Method: Quantitative PCR
  - potency marker: ACAN (mRNA)





HE staining

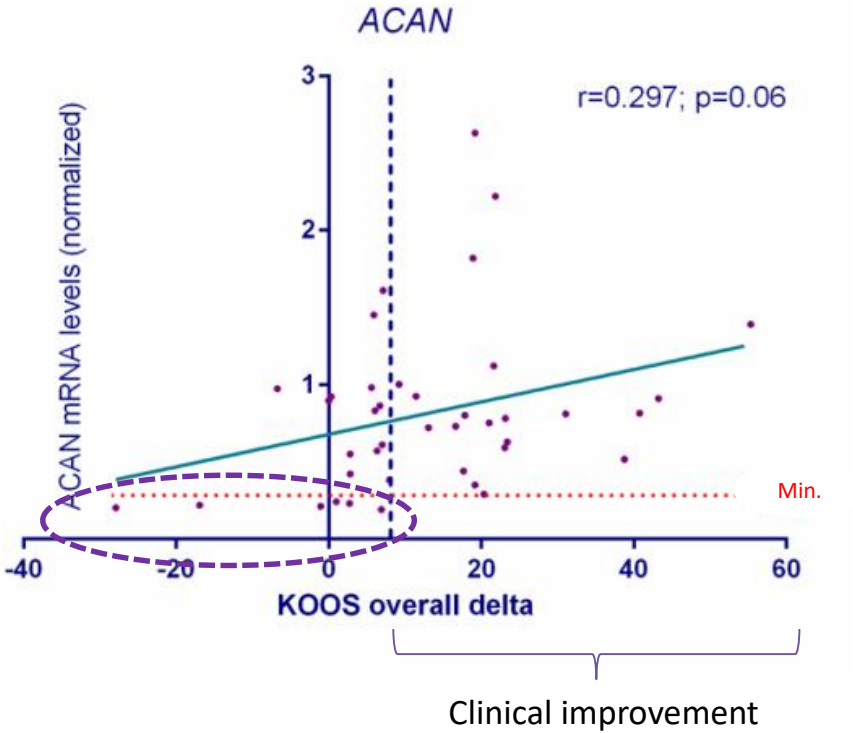
NC – native cartilage
ML – multilayer
RT – regenerated tissue
S – spheroid
SB, subchondral bone

Bartz et al., 2016 (Journal of Translational Medicine)

Release test for ‚Potency‘

Clinical validation

- Assessment of spheroid batches used in Phase II+III clinical trials
  - ACAN mRNA levels
  - Clinical improvement (KOOS>8)
- No statistical correlation found
- Lowest ACAN levels: no improvement



Bartz et al., 2016 (Journal of Translational Medicine)

Cell based therapy for cartilage repair

CMC/Product development – built-in quality

Predictive markers
Operational ranges

Phase II+III clinical trials

- Identify and determine parameters for manufacturing and Quality Control
- Develop specific tests. Determine analytical methods.
- Clinical validation phase: justify release criteria using clinical data

Meldingen aan TRIP

CO.DON AG, Duitsland

DADA, Nederland > TRIP

Pharmacovigilance

Melden van bijwerkingen

• Europees:	PSUR, periodic safety update report	EMA/Swissmedic/MHRA
• Duitsland:	PSUR	Paul-Ehrlich-Institut

- *Product-gerelateerd: ‚dilamination of graft‘*
- *Bijwerkingen die ontstaan tijdens de chirurgische ingreep*
- *Kwaliteit-gerelateerde meldingen: bijv. kontaminatie van transportbuffer*

- Nederland: jaarlijkse berichtgeving aan TRIP
  via DADA consultancy B.V.

Meldingen aan TRIP

Handleiding TRIP

Procurement:
- Bloed
- Kraakbeen (biopt)

Processing:

Serum isolatie, filtratie

Celisolatie, expansie, aggregatie

Application:

ACI

Communicatie:

- Pharmacovigilance CO.DON DE >> DADA NL >> TRIP
- Jaarlijkse berichtgeving:
  - OOS (out of spec) productieproces — cel adhesion/cell viability/proliferation
  - OOS Quality Control — contamination/potency/purity/identity
  - Aantal behandelde patienten, aantal & reden van OOS, tweede biopt

Meldingen aan TRIP

Handleiding TRIP

Procurement:

- Bloed
- Kraakbeen (biopt)

Processing:

Serum isolatie, filtratie

Celisolatie, expansie, aggregatie

Application:

ACI

Product wordt niet vrijgegeven: out of specification

- cQA/release parameter: **purity** waarde is boven de toegestane limiet
- cQA/release parameter: **potency** waarde is onder der toegestane limiet
- cPP/IPC+release parameter: **celkultuur** kultiveringsduur te lang, celexpansie, afbreken van het celkultuur proces
- cQA/release parameter: **steriliteit** (endotoxine, mycoplasma, steriliteit)

Hartelijk dank!

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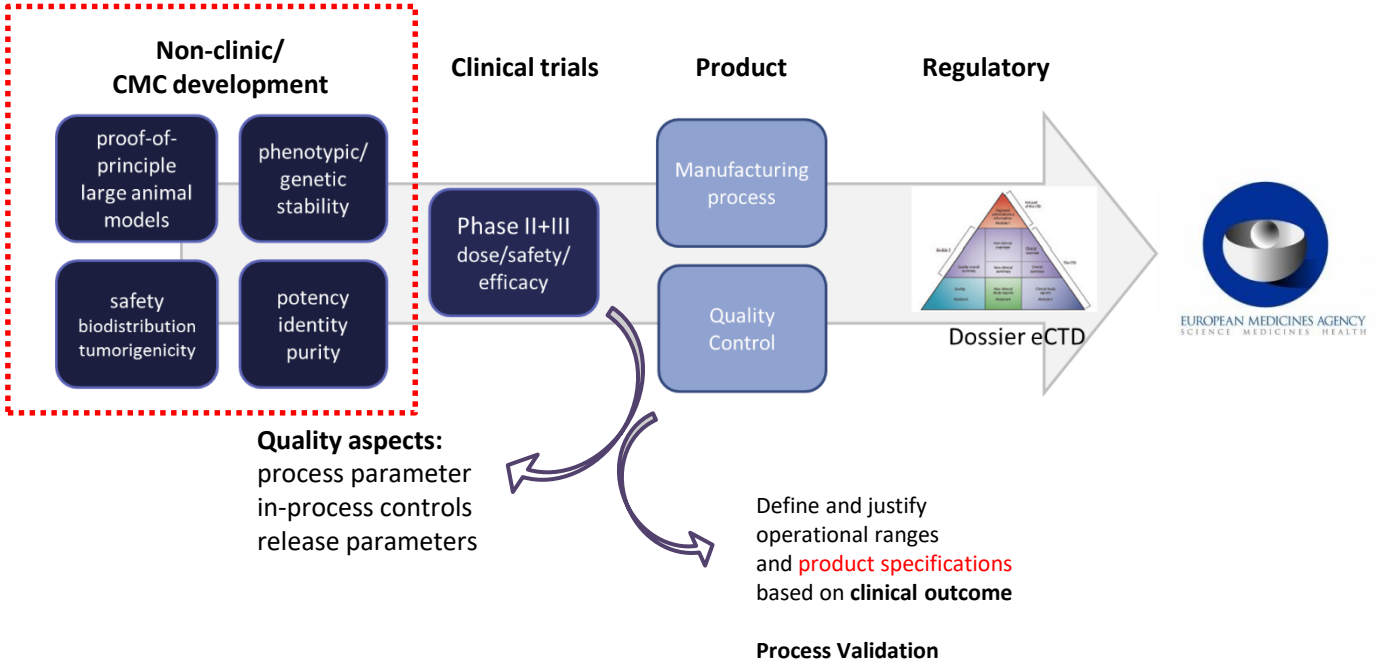
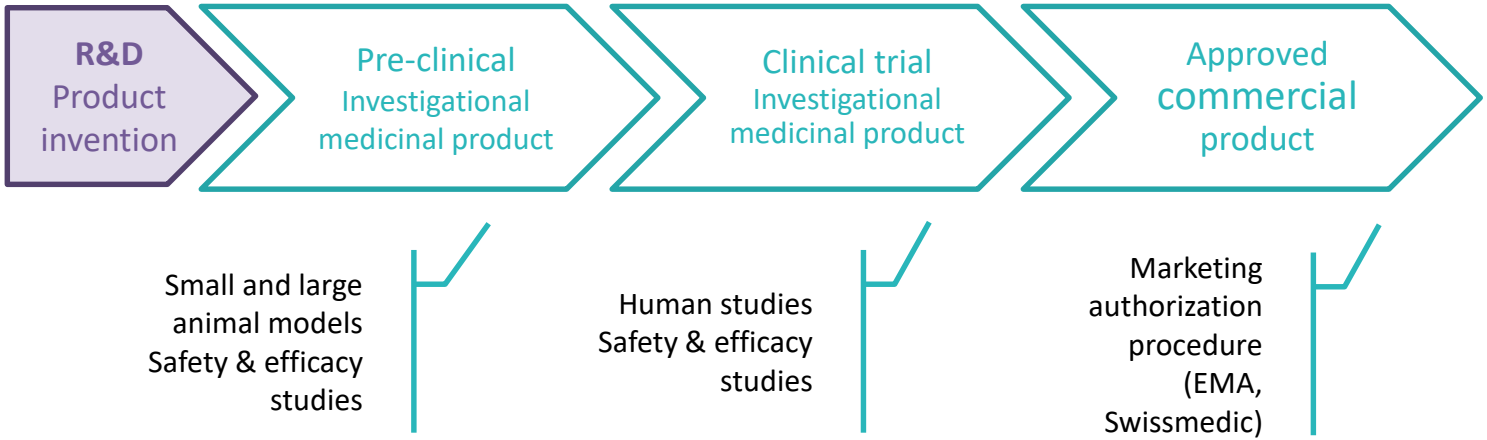
Pharmaceutical Development

Safety and efficacy – Quality by design



Pharmaceutical Development

From invention to commercial product



- Chemicals, raw materials
- Manufacturing process
- Quality Control regime

- ‚Built-in quality'
- Operational ranges
- In-process controls
- Product specifications