HOLOSTEM

Case study: Holoclar

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MISSION AND HISTORY OF HOLOSTEM S.r.l.

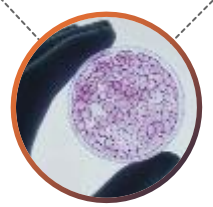
Holostem is a biotechnology company entirely devoted to research, development, manufacture, registration and distribution of Advanced Therapies Medicinal Products (ATMPs) based on cultures of epithelial stem cells both for cell and gene therapy.

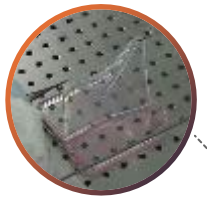
MISSION

DELIVER LIFE CHANGING ADVANCED THERAPIES FOR ALL IN NEED, TOGETHER!

Holostem Terapie Avanzate was founded in 2008 as a spin-off between University of Modena and Reggio Emilia, the academic founders Prof De Luca and Prof.ssa Pellegrini and Chiesi Farmaceutici

In 2015, Holoclar® is the first stem-cell based therapy (limbal stem cell deficiency) to obtain Conditional Approval from EMA





Holostem consolidates its portfolio with gene therapy sperimental products for Junctional and Dystrophic Epidermolysis Bullosa

Holostem Terapie Avanzate enters the process of liquidation in 4Q 2022

In 4Q 2023, Holostem Terapie Avanzate transfers the whole business to the new company Holostem S.r.l.
that is acquired by Fondazione Enea Tech and Biomedical

In 1Q 2024 Holoclar® receveing Full Marketing Authorization from EMA

HOLOCLAR® the first stem cell based ATMP classified as tissue engineered product (TEP)

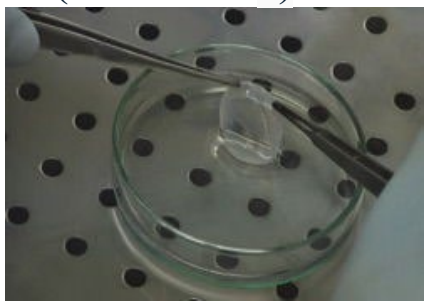
Holoclar is a Stem Cells (SCc)-based treatment used to replace damaged cells on the surface of the cornea

Holoclar consists of a transparent circular sheet of 300,000–1,200,000 viable autologous human corneal epithelial cells. This medicinal product is the result of an industrial process consisting of amplifying the SCs ex vivo from a biopsy sample of 1–2 mm^2 of healthy limbal tissue from the patient who will receive the cellular sheet

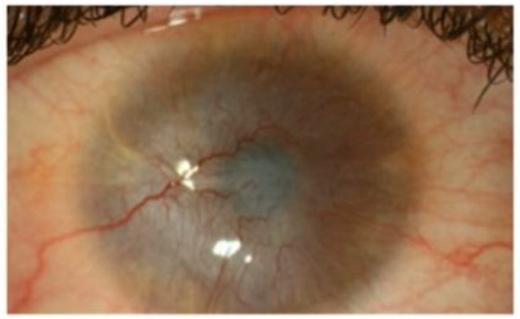
Holoclar®service is distributed and reimbursed by national healthcare system in 8 countries

Holoclar Price Tag:
ITA € 95.000/eye
UK £ 80.000/eye

A cultured sheet of corneal epithelium (Holoclar®)



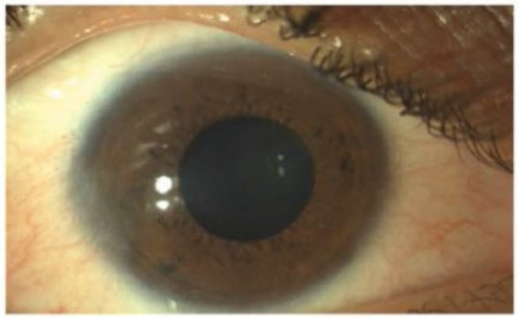
Before Holoclar



Pre-surgery:

- Chemical burn, 3 years from the accident
- No prevoius surgery
- Neovascularization in 4 quandrants with central corneal involvement

After Holoclar



1 year post Holoclar implant:

- Avascular corneal surface with regular and stable epithelium
- Best corrected visual acuity: 0.9

Rama P, Matuska S, Paganoni G, et al. Limbal stem-cell therapy and long-term corneal regeneration. N Engl J Med. 2010;363(2):147-55.

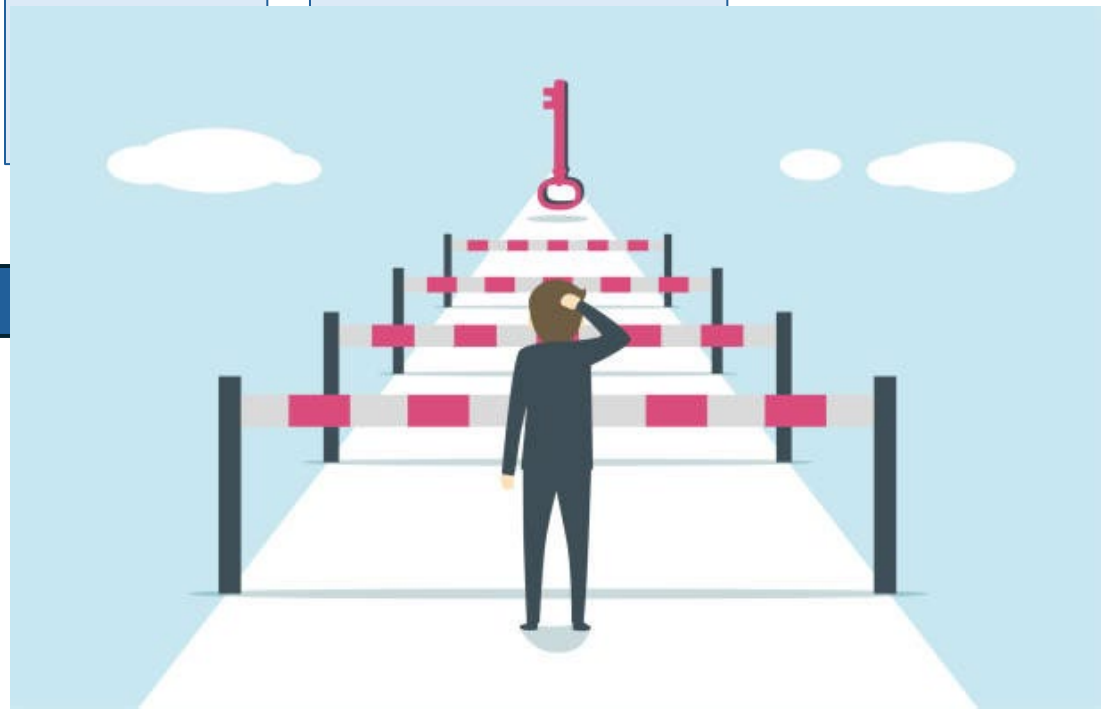
The long and complex authorization process for Holoclar: conditional marketing approval in the EU in 2015

Holoclar was approved **from 3 retrospective studies and 150 patients**

Designed orphan medicinal product by COMP

2008

Defined as advanced therapy medicinal product by ITF



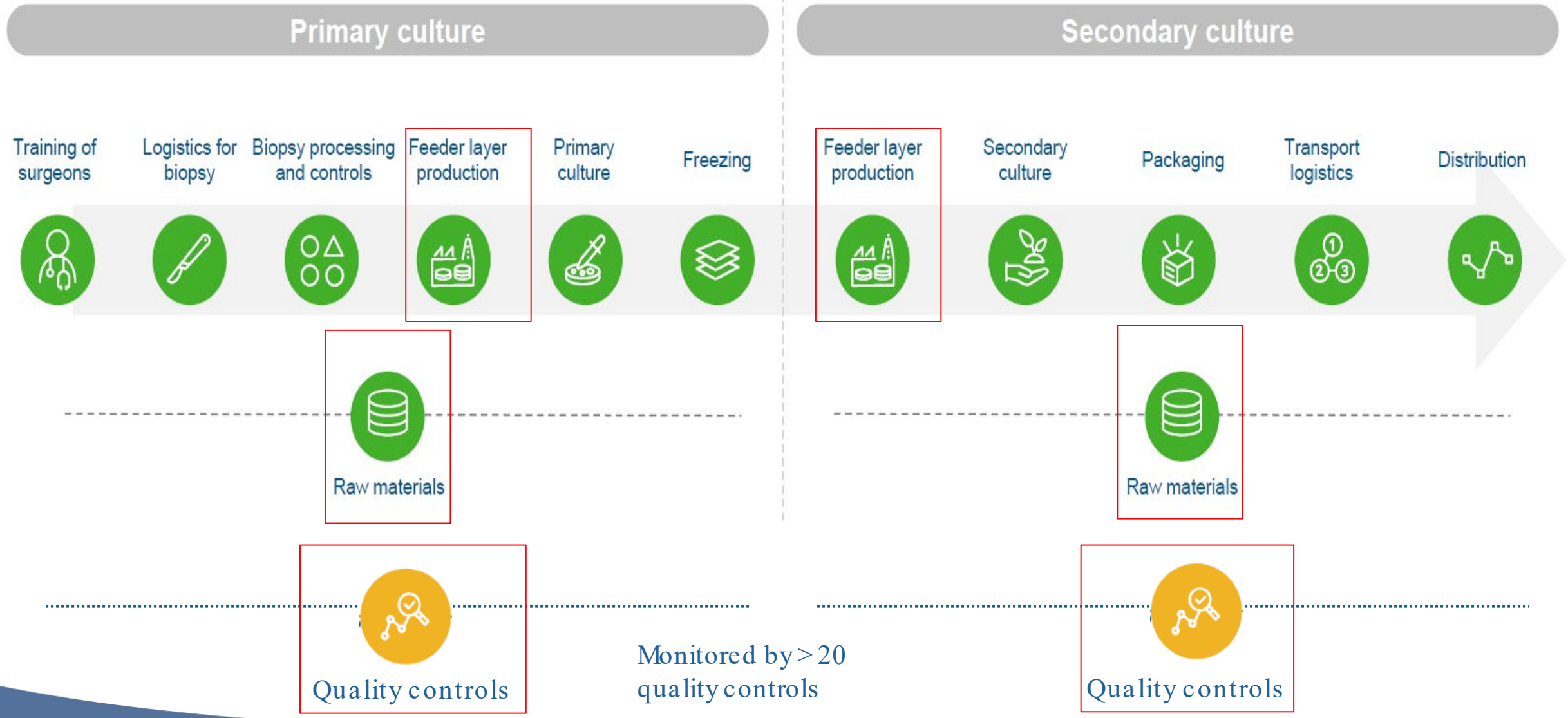
2014 2015

sitive

17 February 2015 Final EC Conditional approval

CAT, Committee for Advanced Therapies; CHMP, Committee for Medicinal Product for Human use; COMP, Committee for Orphan Medicinal Products; EC, European Commission; EMA, European Medicines Agency; ITF, Innovation Task Force; NRG, Name Review Group;PDCO, Paediatric Committee; PEI, Paul Erlich Institute; PIP, Pediatric Investigation Plan

Challenges in Holoclar development from a product quality perspective, which required discussions with regulatory agencies



Quality Challenges: How Holostem Overcame Them

Requirement for GMP-Grade Raw Materials

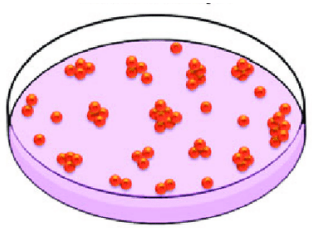
- using GMP-grade raw materials in cell cultures, including stem cells, is essential for regulatory compliance and product quality.
- non-GMP components, such as animal- or human-derived serum, culture media, and growth factors, should be replaced with GMP alternatives where available.

Mitigating risks through controls on raw materials, validation, and adherence to GMP standards is crucial.

Implementation of a rapid sterility test which is suitable to deliver results prior to administration of Holoclar.

- essential for ensuring patient safety, regulatory compliance, and product quality prior to administration of Holoclar
- cell-based products added complexity to sterility testing

The rapid sterility test was successfully implemented, providing results within three days.



Implementing a method to quantify 3T3 feeder contaminant cells is crucial due to concerns about the risks of contamination, immunogenicity, and the transmission of infectious agents.

- the use of a feeder layer can complicate the consistency of the manufacturing process for products like Holoclar.
- detailed characterization of feeder cells, including their origin, growth conditions, and potential contaminants, is essential to evaluate the safety and efficacy of Holoclar

The method to quantify 3T3 feeder contaminant cells in both the drug substance (DS) and drug product (DP) has been successfully implemented.

Holoclar's Journey: Navigating Challenges and Achievements in Developing a Novel ATMP in a Shifting Regulatory Landscape

Conditional approval: It received conditional marketing approval, reflecting the challenges encountered throughout the development process

Regulatory environment: This experience highlighted the critical role of regulatory frameworks in promoting innovation

Safety and efficacy: Holoclar exemplified the balance between advancing new treatments and maintaining high standards for safety and effectiveness

Model for future ATMPs: Holoclar set a valuable precedent for the development of additional advanced therapies

Lessons learned

-Holoclar provided valuable insights to regulators and developers on the complexities of advanced therapies
-Developers learned the importance of navigating an uncertain landscape through close cooperation with regulatory bodies.

Holoclar: The regulatory process for Full Market Approval in 2024

2015
EMA
CONDITIONAL
APPROVAL

2016 2017 2018 2019 2020 2021 2022 2023

Oct'15 — Mar '22

HOLOCORE (n=69*)
Assessment of efficacy and safety of Holoclar;
efficacy endpoint based on restoration of corneal epithelium

Dec '17 — Mar '23

HOLOCORE-FU (n=42)
Long-term efficacy and safety assessment after one or two treatments with Holoclar and with/without Keratoplasty: min 12-max 66 months follow-up**

Oct'16 — Dec'28

HOLOSIGHT (n=90)
Assessment of safety and efficacy in standard clinical practice, build-up of a PASS study with long-term of safety data (AEs), 5 years after first transplantation

2024
22 February
FULL MARKET
APPROVAL

* 69 adults + 4 minor 6-17 treated in HOLOCORE; **since inclusion in Follow-up study (+12-m after Holoclar implantation)

Conclusion

The Holoclar experience exemplifies the value of positive interaction between industry and regulators in a complex field like stem cell therapy for rare, unmet medical needs, leading to a success story.

Take home messages

The relationship with the regulatory authorities from the first development phase is mandatory

Monitor every stage of the supply chain to ensure that all raw materials, reagents, product components, and manufacturing equipment comply with the required standards

Early product development should prioritize GMP-grade raw materials and, when possible, animal-free alternatives, while ensuring researchers are trained on regulatory rules from the start of their education

Streamline processes and quality controls through customized automation, standardization and scale up production to ensure the sustainable long terms of ATMPs

Thank you for your attention