Transparency-Driven Partnerships for Shared Success – iPSC journey

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11 JUNE 2025

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Cell and Gene Therapy Network

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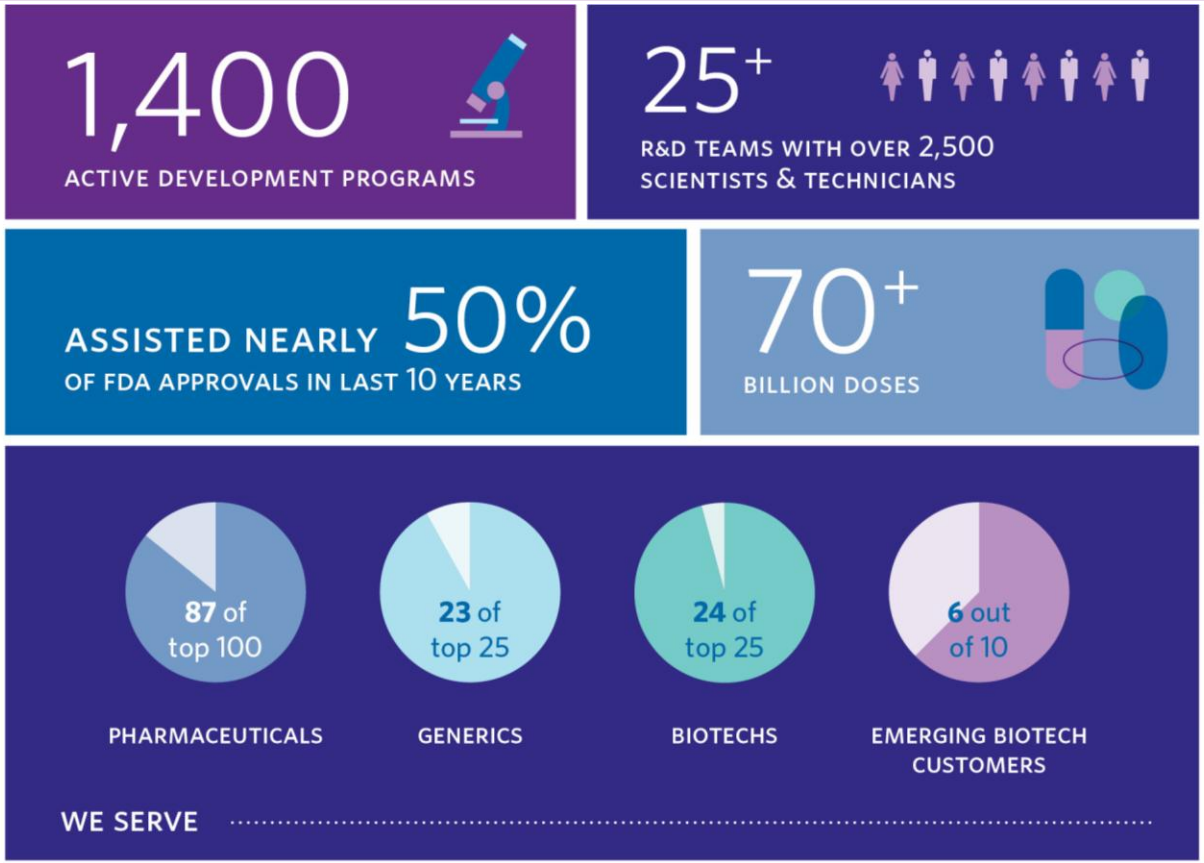
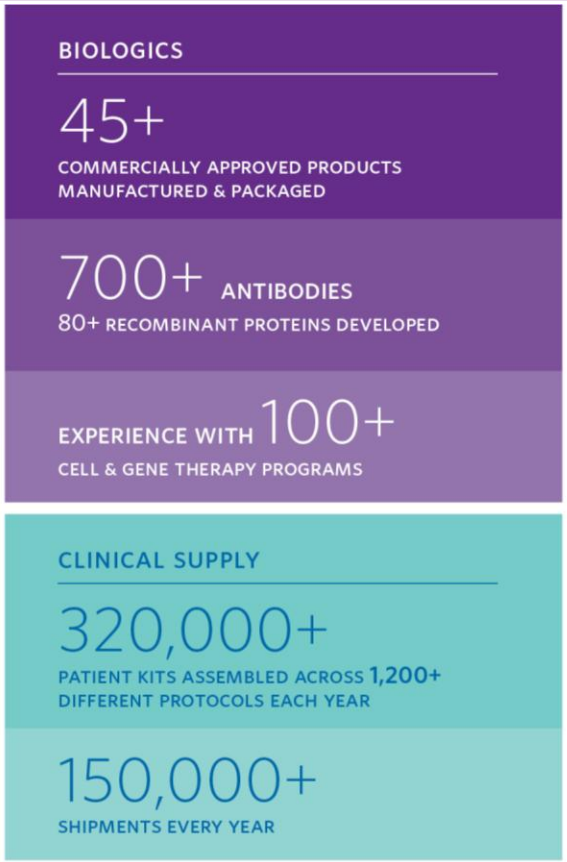
CDMO Expertise & Scale to Help you Succeed





Our CGT Campuses in EU and US

BALTIMORE, MD
U.S. CAMPUS GT/pDNA

BWI -1 BWI-2

Biopark

PRINCETON, NJ
U.S. CAMPUS CT

GERMANY, BELGIUM
E.U. CAMPUS CT/pDNA

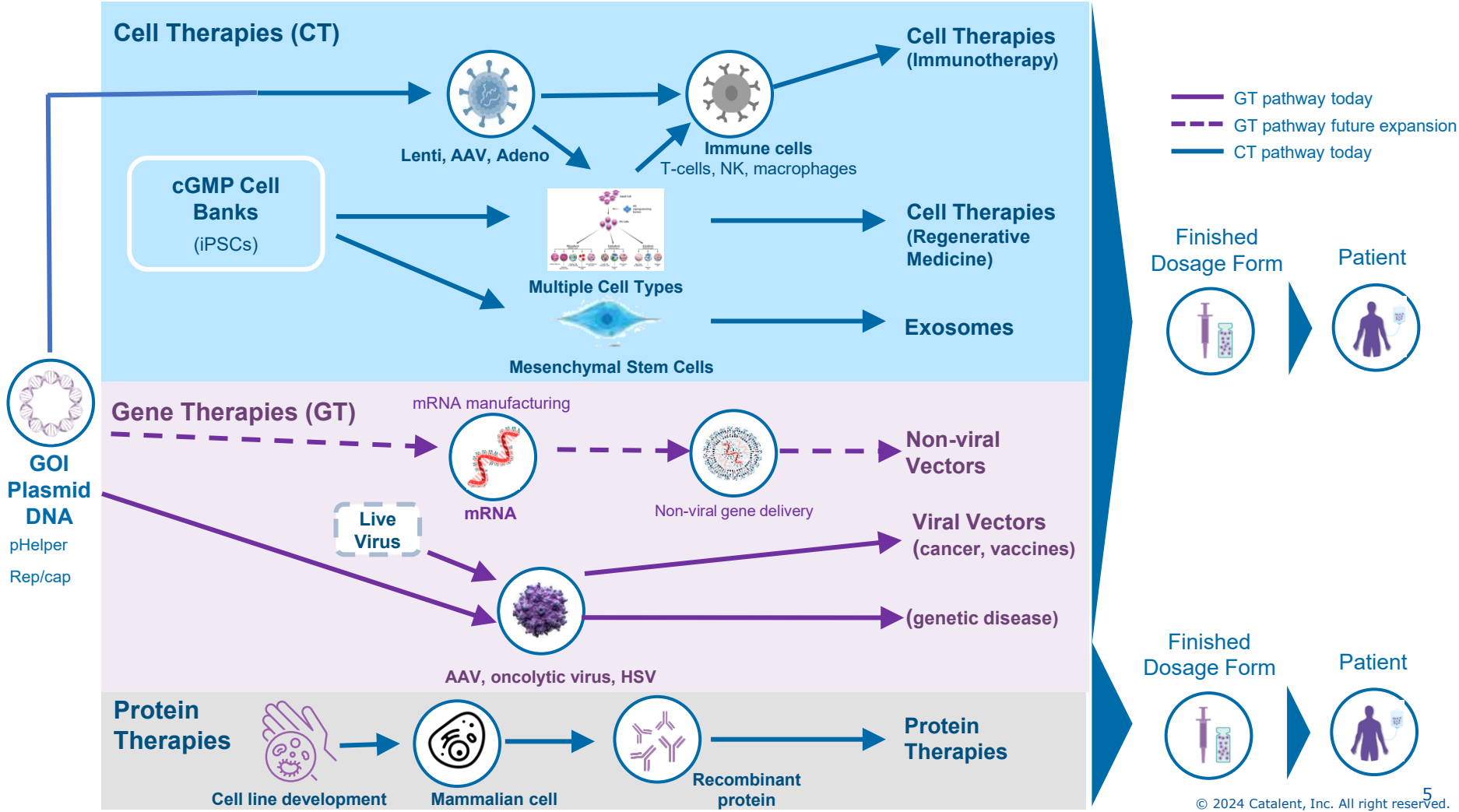
Gosselies West

Gosselies East

Gosselies CATC

Gosselies Plasmid

NEW:
Dusseldorf, Germany



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iPSC overview

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Developed process

GMP process to transfer

hIPSC line MCB generation

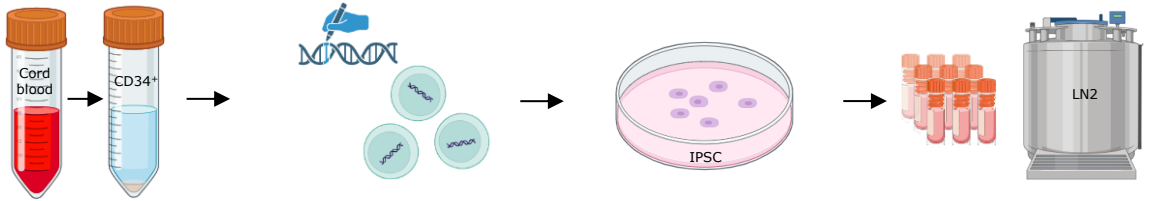
10 weeks in cleanroom

Donor collection and CD34+ selection

Reprogramming

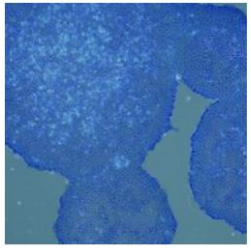
hIPSC line generation & characterization

hiPSC line MCB and storage

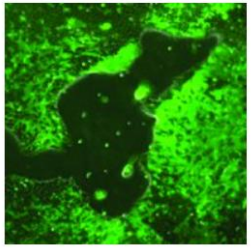


Characterization Assays	
▪ Sterility	▪ Cell identity
▪ Endotoxin	▪ Cytogenetic analysis
▪ Mycoplasma	▪ Mutational burden
▪ Viral safety	▪ Flow cytometry
▪ Vector elimination	▪ Immunofluorescence
▪ Cell recovery from MCB	▪ RT-qPCR analysis
▪ Morphology	▪ 3-germ layer differentiation

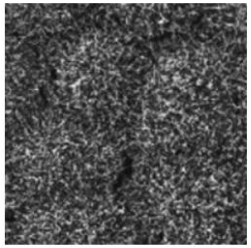
Differentiation potential



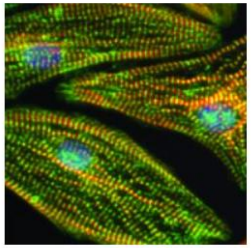
Off-the-Shelf GMP iPSC Lines



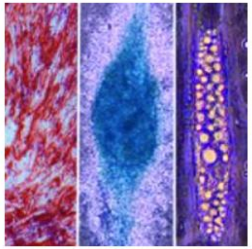
Gene Editing of iPSCs



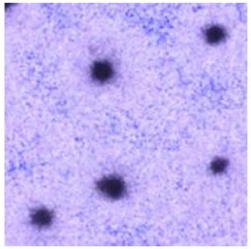
RPE Differentiation of iPSCs



Cardiac Differentiation of iPSCs



iPSC-Derived MSCs



Immune Cells

iPSC line	Smooth muscle	Renal	Cardiac	MSCs	NK cell	T cells	MΦ	Endothelial	Hepatic	Pancreatic	Neural	RPE cells	Gene editing
R23	+	+	+	+	+	+	+	+	+	+	+	+	+
R26	+	+	+	+	+	+	+	+	+	+	+	+	+
R34	+	+	+	+	+	+	+	+	+	n/d	+	+	+
R35	+	+	+	+	+	+	n/d	+	+	n/d	+	+	n/d
R36	+	+	+	n/d	+	+	n/d	+	+	n/d	+	+	n/d

Cell lines available

iPSC line	Donor origin	HLA type	Sex	Blood group	Status	Remarks regarding donor eligibility
R23	EU	homozygous	female	A Rh negative	GMP cell bank released; R&D evaluation stocks available	EMA-compliant, mitigation testing addressing FDA regulations performed
R26	EU	homozygous	male	0 Rh negative	GMP cell bank released; R&D evaluation stocks available	EMA-compliant, mitigation testing addressing FDA regulations performed
R34	EU	heterozygous	male	A Rh positive	GMP seed stocks produced, QC pending, R&D evaluation stocks available	EMA, FDA, and PDMA-compliant (strategic donation)
R35	US	heterozygous	male	0 Rh negative	GMP seed stocks produced, QC pending, R&D evaluation stocks available	FDA-compliant, assessment for EMA-specific regulations pending
R36	US	heterozygous	female	0 Rh negative	GMP seed stocks produced, QC pending, R&D evaluation stocks available	FDA-compliant, assessment for EMA-specific regulations pending

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Challenges

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Timeline iPSC

2015-16

Process developed with Partnership for Cord Blood Unit supply in Germany

2018

Commercial License for iPSC after discussion with PEI and German Authorities

2020

Process and analytical methods locked and validated for commercial grade

2022

Clients started discussions and submission in EU and also in US

2022

Exemption request needed about EU Donor used in the US

21 CFR 1271

2022

Partnership with US Cord Blood supplier

2023

Quality and Regulatory Partnership - Exemption request granted

2023

Importation in EU of US Human Body Material – Tissue Establishment

2024

Cell lines – EU/US Compliant

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1. Donor Eligibility

Exemption Request – US Requirements

CONTEXT:

"Request for Exemption under 21 CFR Section 1271.155(a) for the use of the iPSC line in the manufacture of cell therapies"

21 CFR Section 1271.155(a) → General. You may request an exemption from or alternative to any requirement in subpart C or D of this part.

→ Subpart C: DONOR ELIGIBILITY

(a) *Testing for relevant communicable diseases is required.* To adequately and appropriately reduce the risk of transmission of relevant communicable diseases, and except as provided under § 1271.90, if you are the establishment that performs donor testing, you must test a donor specimen for evidence of infection due to communicable disease agents in accordance with paragraph (c) of this section. You must test for those communicable disease agents specified in § 1271.85. In the case of a donor 1 month of age or younger, you must test a specimen from the birth mother instead of a specimen from the donor.

(b) *Eligible donor.* A donor is eligible under these provisions only if:

(1) Donor screening in accordance with § 1271.75 indicates that the donor:

(i) Is free from risk factors for, and clinical evidence of, infection due to relevant communicable disease agents and diseases; and

Partnership Sponsor - Manufacturer

Exemption dossier included :

- Full Medical History and Screening Questionnaire
- All certificates, licenses, FEI, CE Marked, …
- Donor testing performed equivalent to 21 CFR 1271 at the time of material collection
- Two tests on cord blood were conducted using in-house tests approved by PEI (German)

Focus was on West Nile Virus, Zika Virus and Transmissible Spongiform Encephalopathies.

- At the time of donation, testing not required
- Evaluation needed and CLIA certified laboratory
- Samples from Mother blood and Cord Blood

Partnership Sponsor - Manufacturer

WNV

- Medical Questionnaire – No travel
- Literature used for isolated WNV cases
- WNV testing required in 2018
- First case in Germany reported in 2019
- Testing performed by a CLIA lab on the iPSC material

ZIKV

- Medical Questionnaire – No travel
- Literature used
- No report case in Germany
- Germany does not have the mosquito that can spread Zika
- Testing performed by a CLIA lab on the iPSC material

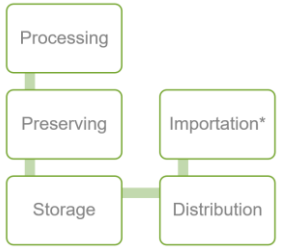
TSE

- Medical Questionnaire :
  - presence of Creutzfeldt-Jakob disease (CJD) within the family
  - received transplants or substances (e.g., hormones) of human origin
  - suffering from diabetes
- Up to and including 2020, no cases of variant CJD have been observed in Germany
- Manufacturing compliant to EMA/410/01

Risk determined as very low

2. Intermediate Structure for GMP

Intermediate structure



Where HBM come from?

- Deceased donor/patient
- Living **consentient** donor/patient

Safety issue

HBM carries the risk of spreading communicable diseases (e.g. hepatitis, AIDS, etc), which should be avoided with a severe selection of donors and ensuring traceability.

Ethical issue

Donor/patient have to know what the material they are donating will be use for

And confidentiality on their identity and any other sensitive information should be respected

Questions to ask:
What the HBM will be used for?

Non-human application

Goes to the Biobank

1.Reception
2.Update the register
3.Release HBM to R&D lab

Human application

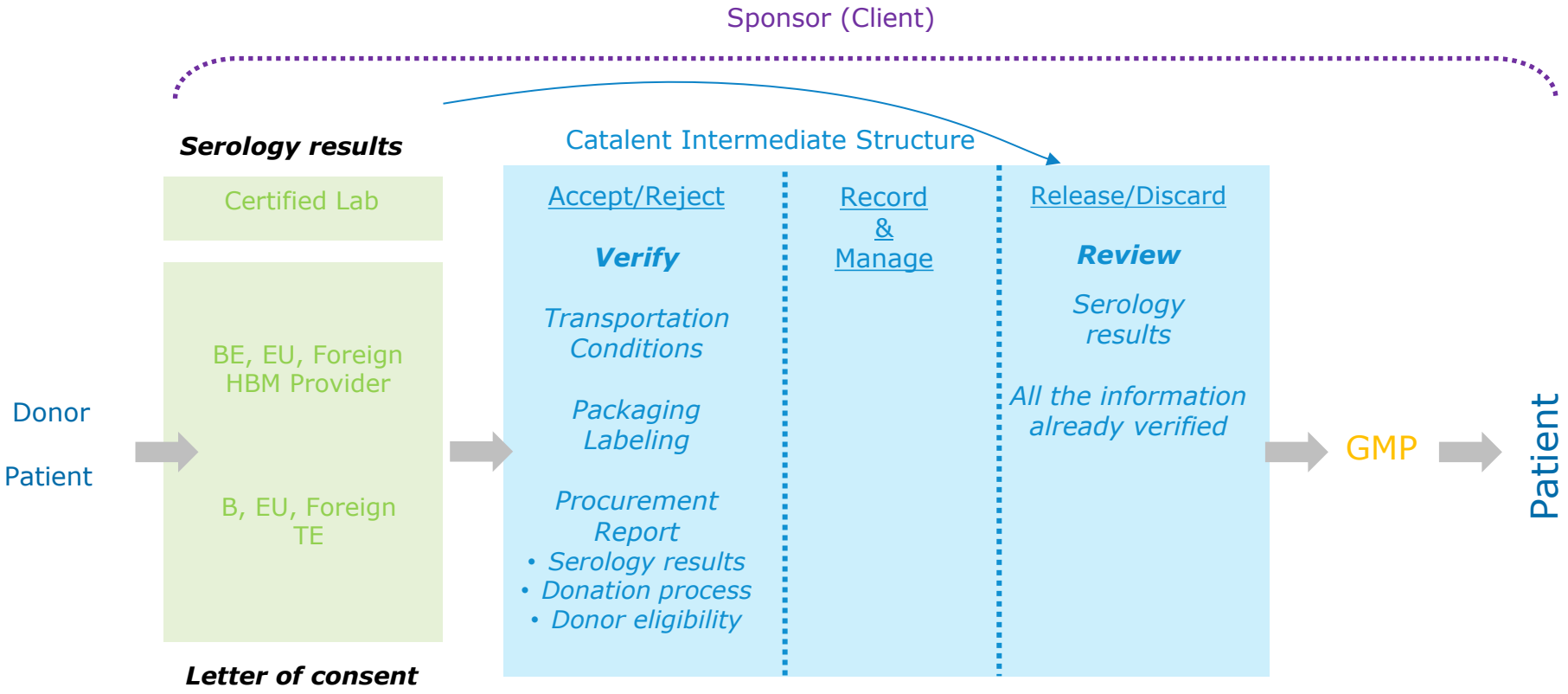
Autologous ATMP

Allogenic ATMP

Goes to the Intermediate Structure

1.Reception
2.Update the register
3.Release HBM to GMP facility

Intermediate structure



Intermediate Structure Challenge – EU Importation

In Europe

The specific technical quality and safety requirements for samples of cord blood are regulated by four directives (2004/23/EC, 2006/17/EC, 2006/86/EC and 2002/98/EC)

Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on **setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells** → Main for US Cord Blood importation topic.

Step for importation to Catalent Gosselies

- **Quality questionnaire** answered by US Supplier
- **Audit** of the Cord Blood supplier
- **Testing** requirements EU – US in a QTA (with client and HBM supplier – Three-Way QTA feasible)

- **Submission** of the request to the authorities
- **Questions** from authorities about the request
- **Acceptation or Rejection** by the EU authorities

6 months process

Applicable by **AUG 7, 2027,** we have the new **EU SoHO Regulation 2024/1938** (published on **JUL 17, 2024)** as it consolidates and modernizes the legal framework for all **Substances of Human Origin (SoHO),** including cord blood cells.

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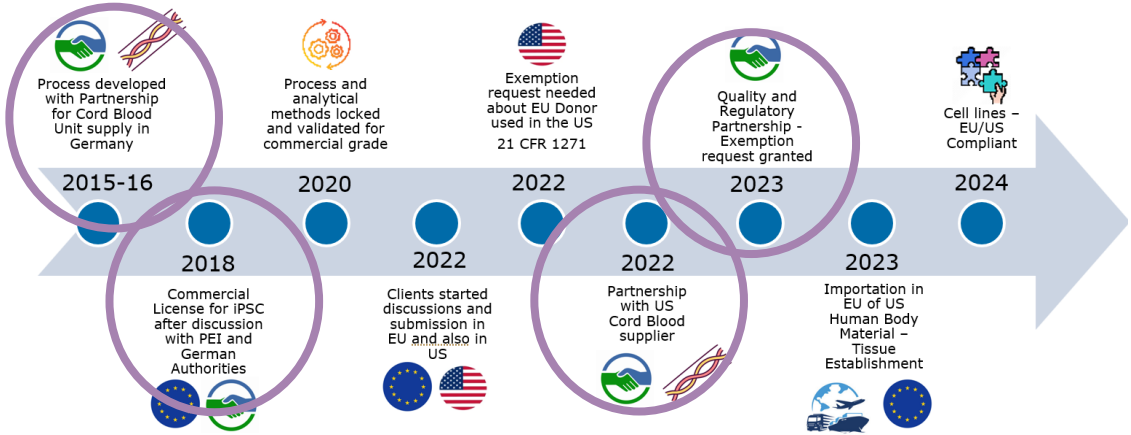
Partnership is key



True partnership thrives on the foundation of transparency, where open communication and mutual trust illuminate the path to shared success

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Thank you

discover more.

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