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# Introduction to ATMP manufacturing

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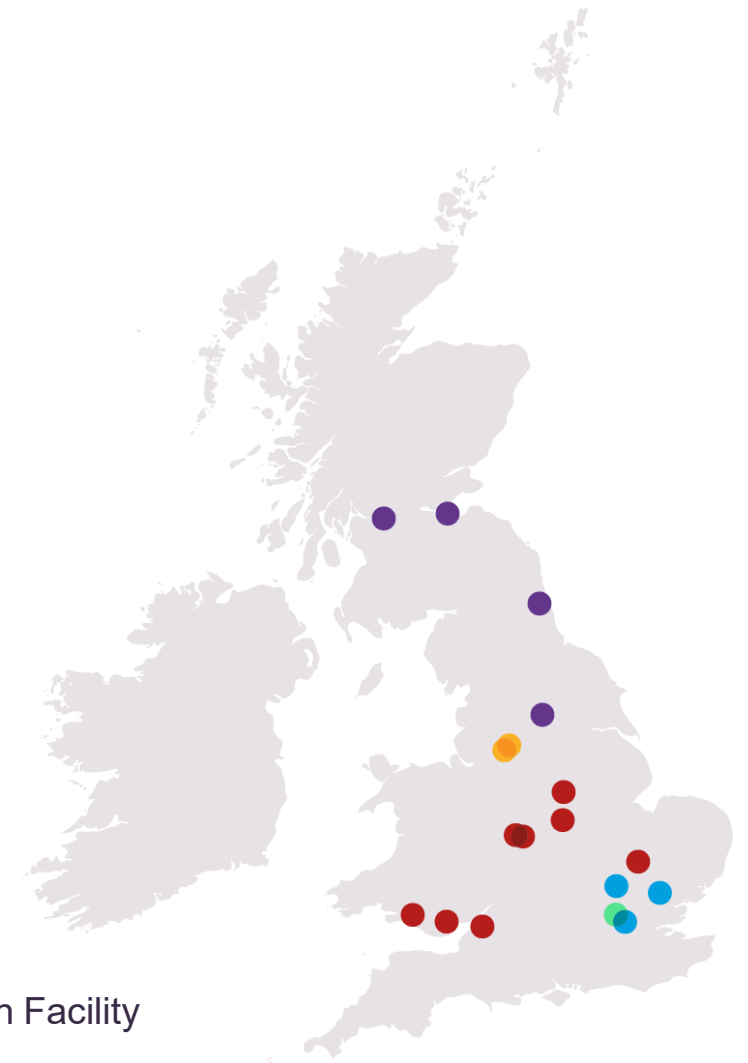
***Ivan Wall,***

Professor of Regenerative Medicine, Cell & Gene Therapy Bioprocessing, Aston University

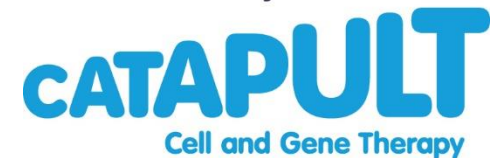
***Chaired by Michelle Davies***

Advanced Nurse Practitioner and Interim Operational Lead, The Christie NIHR Clinical Research Facility

Funded by



Coordinated by



# Who are LAT and the ATTCCs?



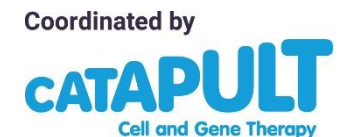
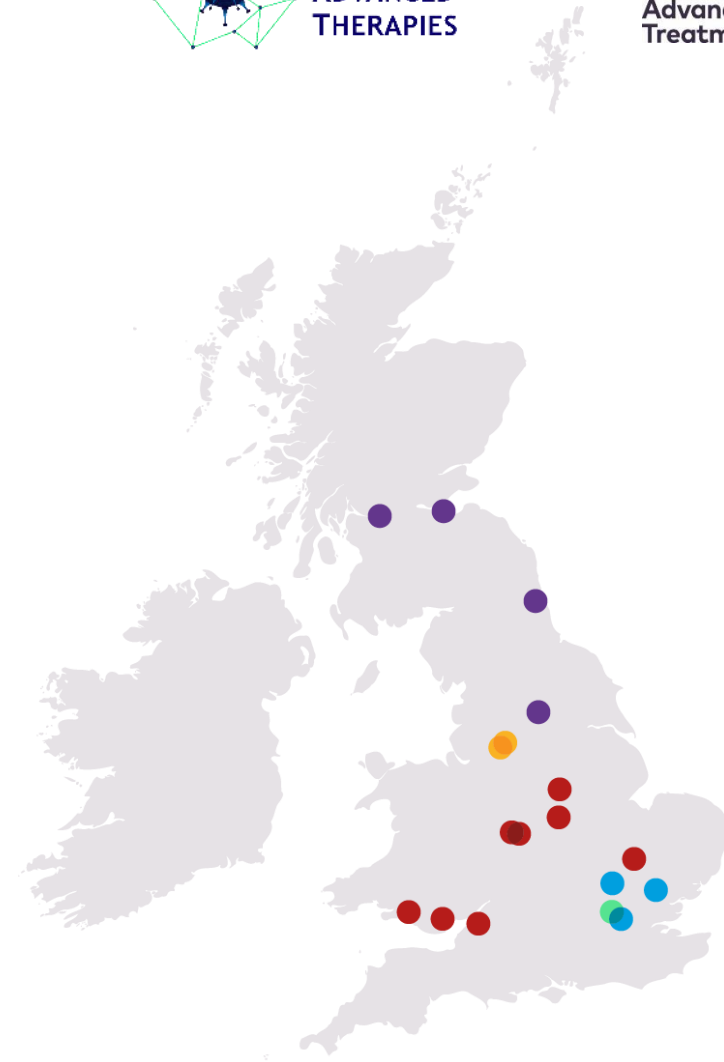
The ATTIC (Advanced Therapy Treatment Centre) network is funded by Innovate UK and the Industrial Strategy Challenge Fund

London Advanced Therapies (LAT) is funded by Research England

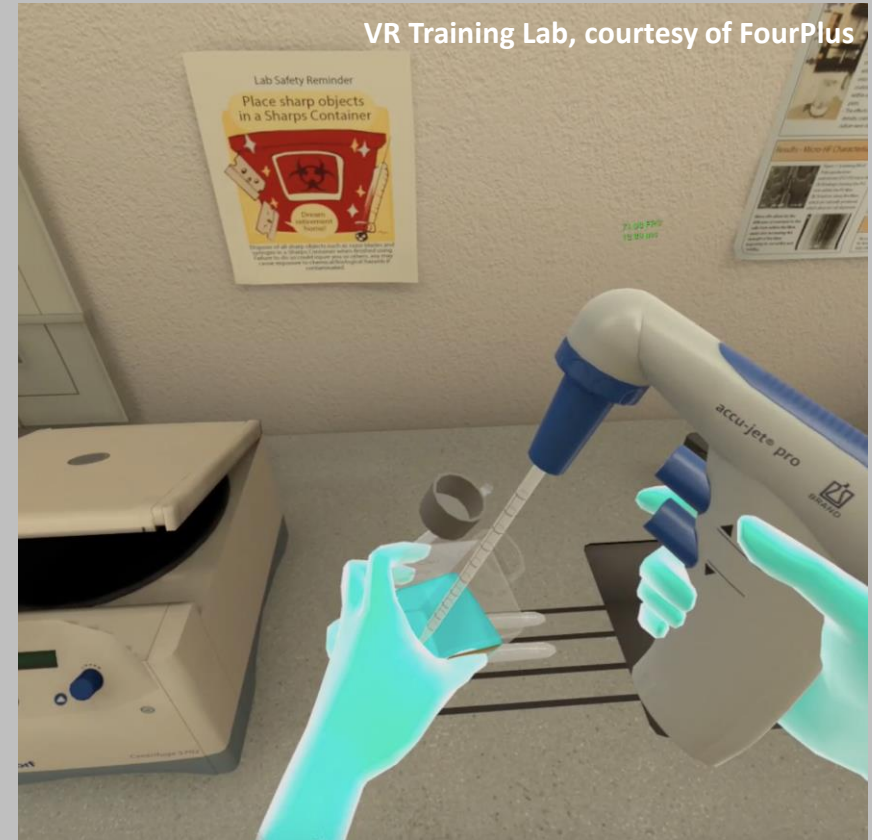
The centres are working together, along with the Cell and Gene Therapy Catapult to specifically look at the training requirements for the current workforce and what needs to be put in place for them to be ready to deliver the treatments that are currently being developed.

This series of webinars is designed to help increase the awareness of advanced therapies and their impact in the clinic

Find out more at <https://www.theattcnetwork.co.uk/>



# Introduction to ATMP Manufacturing



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# Why is manufacturing science important for ATMPs?

**Discovery science is not  
robust, consistent or scalable**



# The Challenge of Manufacturing Medicines

The penicillin story:



**Discovery Science**  
Small scale  
Highly variable  
Lacks Consistency



**Commercial Production**  
Industrially Scalable  
Consistent Quality  
Cost-Effective



**Stable Product**  
Long shelf life  
Easy Storage / Distribution

# ATMPs... Are Diverse

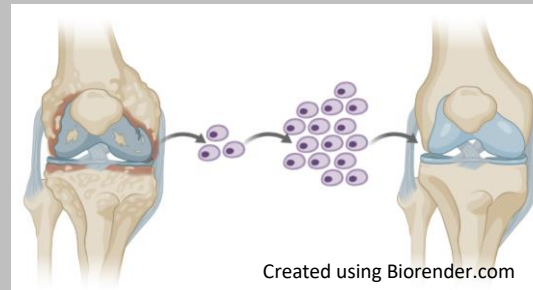
Advanced therapy medicinal products (ATMPs) are medicinal products that are either:

## Gene Therapy



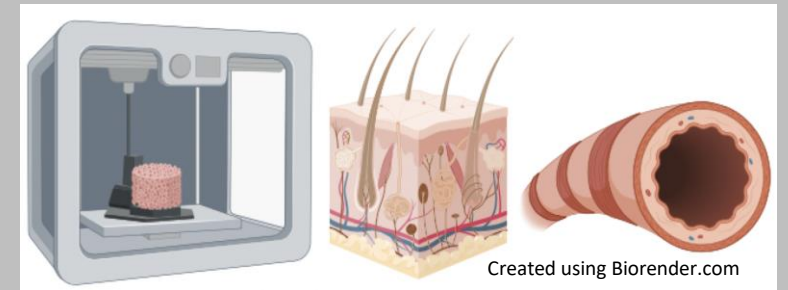
(e.g. CAR-T cells)

## Somatic Cell Therapy



(e.g. stem cell therapies;  
regenerative medicine)

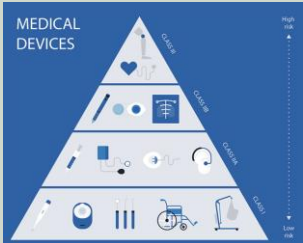
## Engineered Tissue



(e.g. skin, airways)

# ATMP Manufacturing is Challenging

## Devices

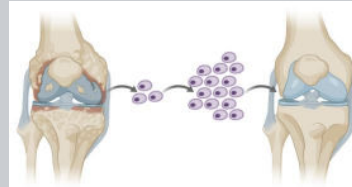
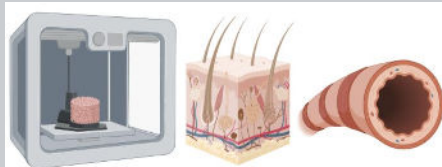


Medical Devices

## Medicinal Products

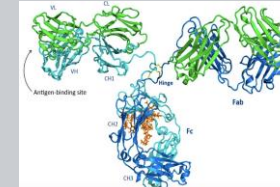
### Manufacturing Complexity / Variability

- Lack of defined manufacturing processes
- Lack of defined regulatory and clinical development pathways
- Lack of defined prescribing, dispensing and delivery protocols



Well established:

- Manufacturing processes
- Regulatory / clinical development paths
- Prescribing, dispensing and delivery



ATMPs

Engineered Tissues

Cell Therapies

Gene Therapies

Biotech

e.g. recombinant proteins

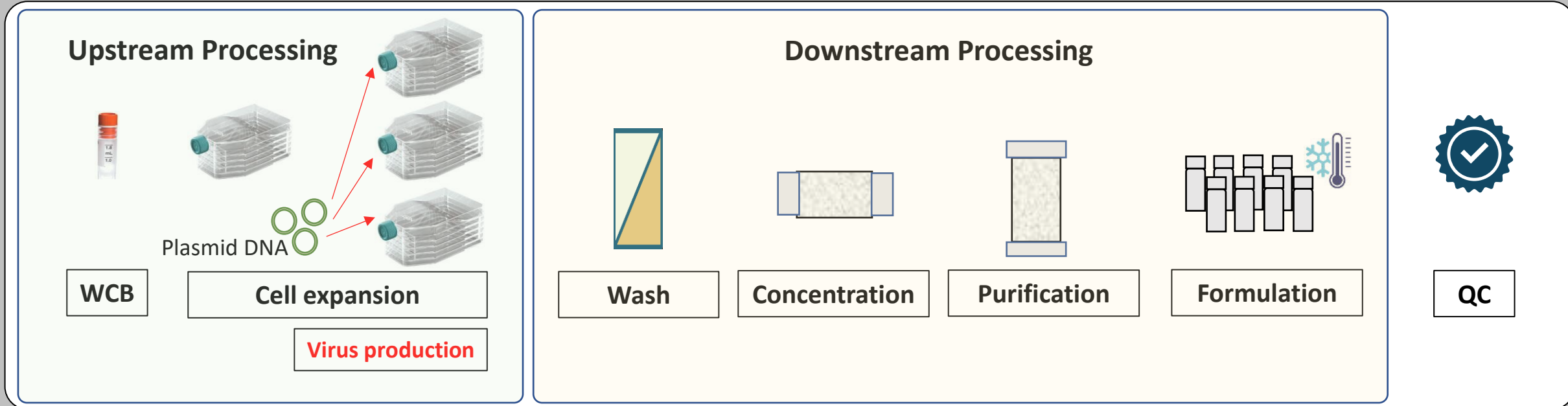
Pharmaceuticals

e.g. small molecule drugs

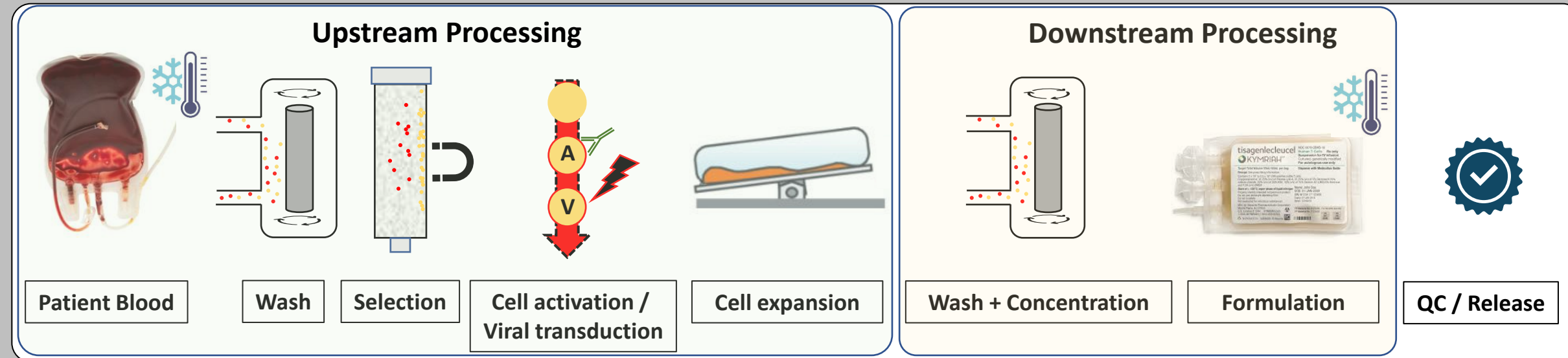


# Example of Manufacturing Pathway (CAR-T)

Viral Vector



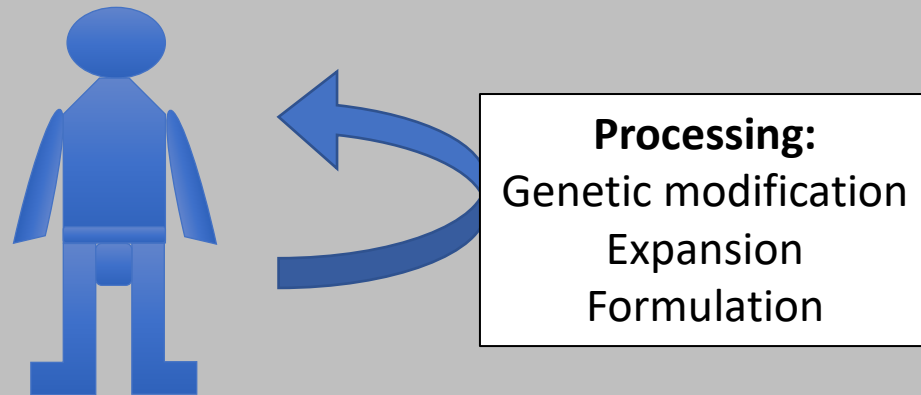
Autologous T-cells





# Autologous versus allogeneic therapies

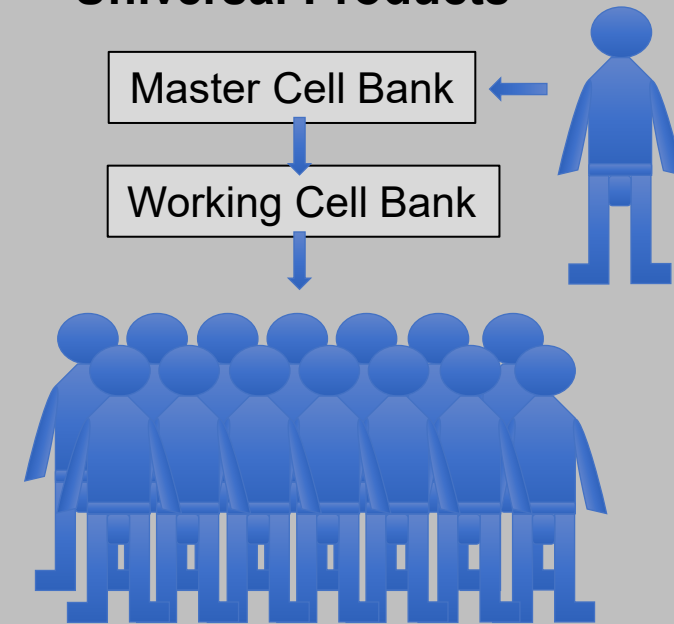
## AUTOLOGOUS Personalized Medicine



### Principles:

- Donor and recipient are the same person
- Small scale (one patient dose / manufacturing lot)
- Point-of-care manufacturing (typically)
- Service-based model
- Costly due to individualized manufacturing costs
- Generally better safety profile due to cell compatibility

## ALLOGENEIC Universal Products



### Principles:

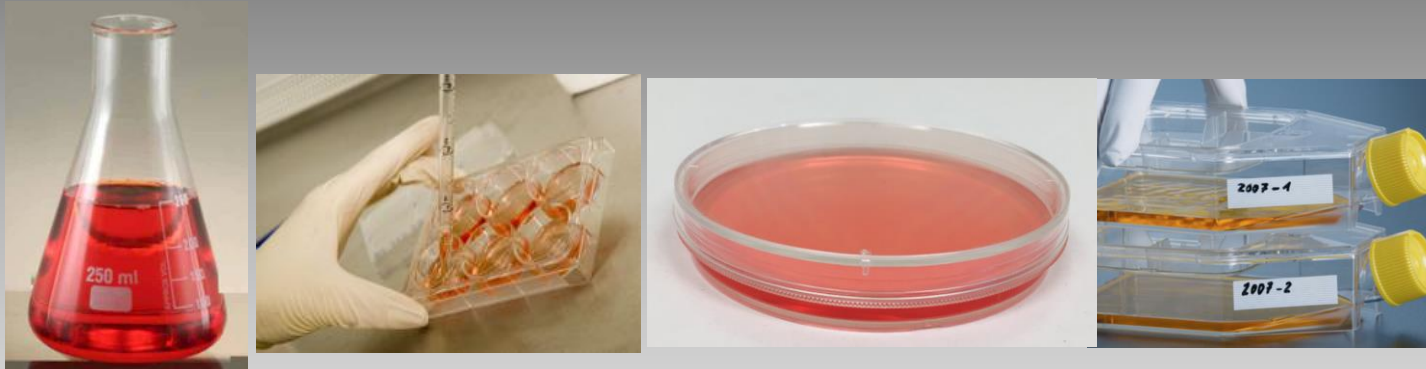
- Donor and recipient are different
- Potentially large scale (many patient doses / manufacturing lot)
- Closer to existing pharma business model
- More cost-effective?
- Risk of rejection and need for immuno-suppression

# Manufacturing Cell and Gene Therapies

## Platform

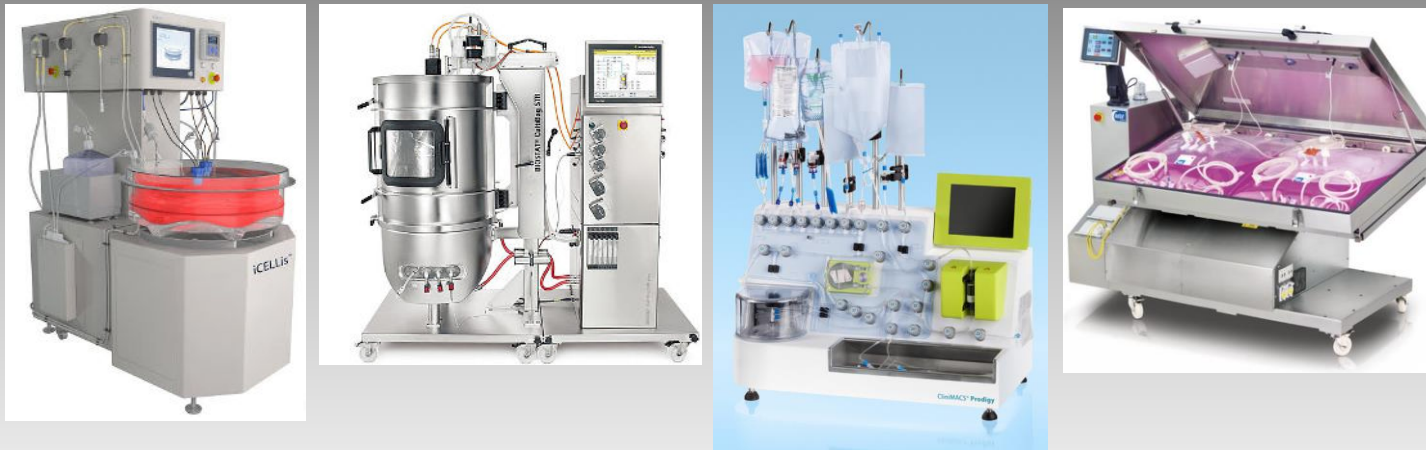
## Characteristics

### Discovery Science



- Open process
- Small scale
- Manual
- Multiple operator interactions
- Contamination risk
- Lack of consistency

### Commercial Platform



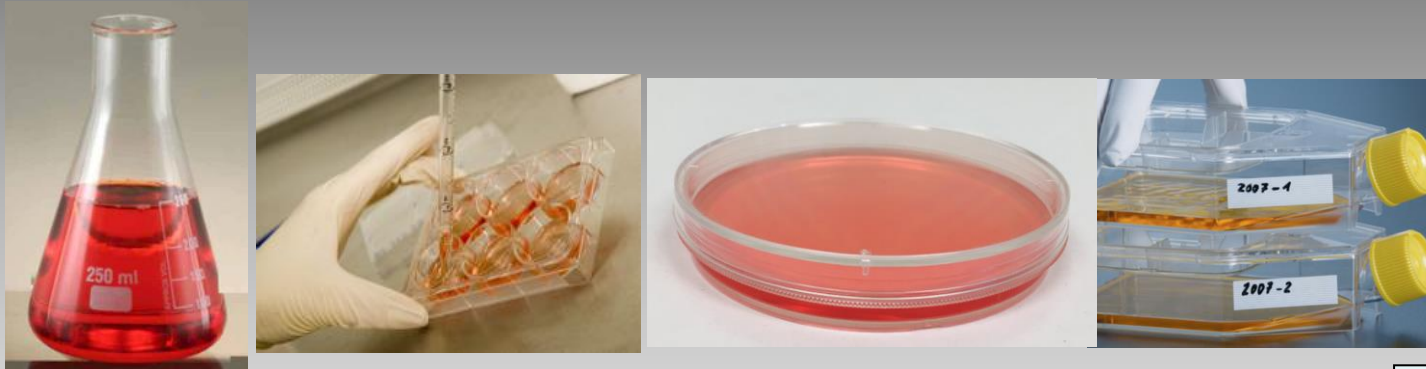
- Closed process
- Small/Large scale
- High cost
- Automation
- In process monitoring/sampling

# Manufacturing Cell and Gene Therapies

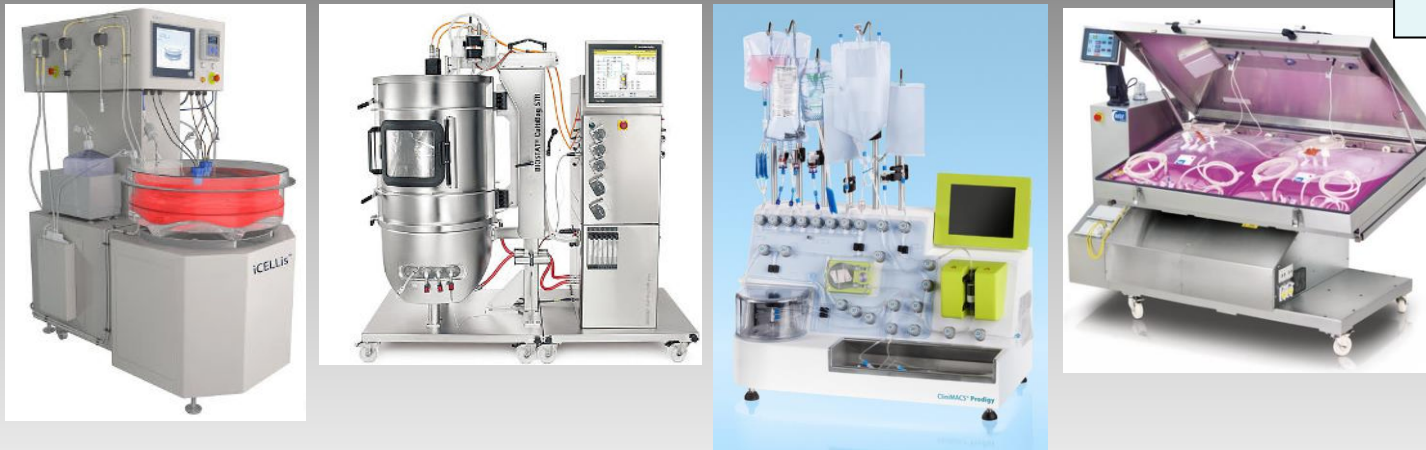
## Platform

## Product

Discovery Science



Commercial Platform

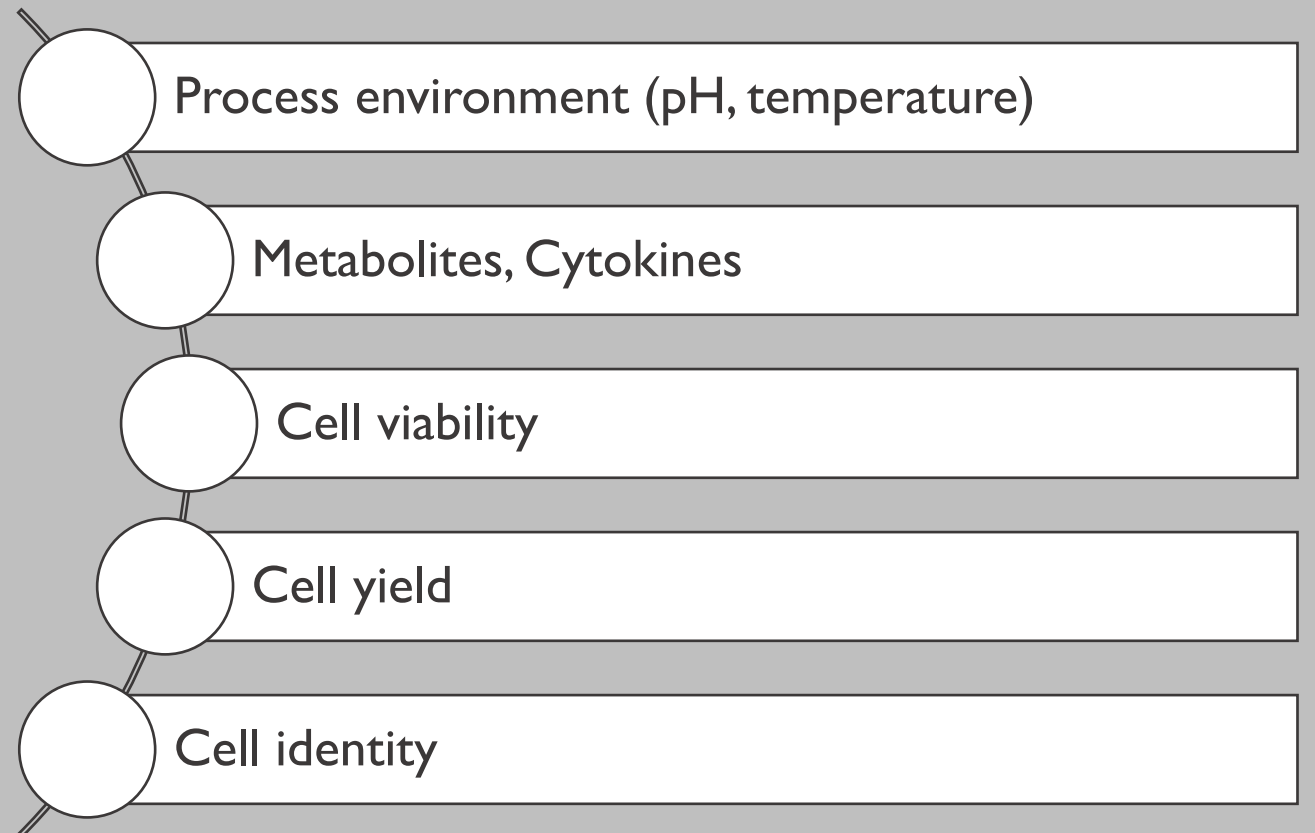
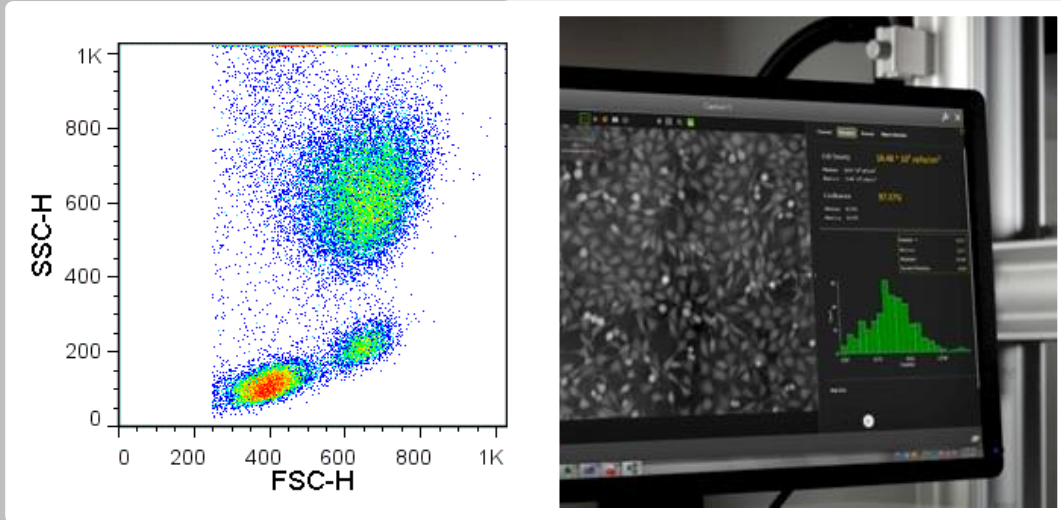


“Correct” Identity Profile  
Consistency quality



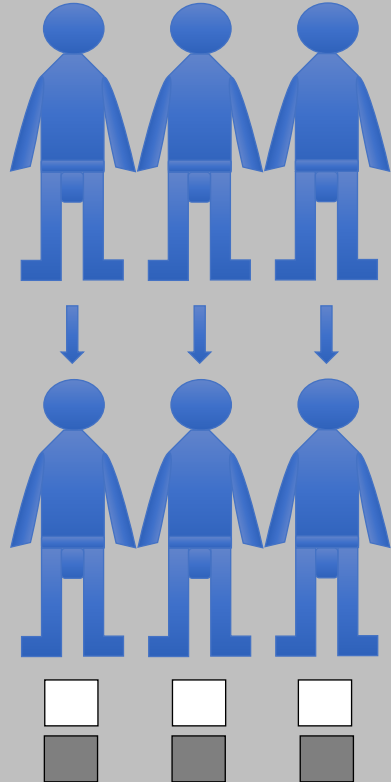
Critical Quality Attributes:  
Safety  
Purity  
Identity  
Potency

# Analytics and Monitoring



# Impact of QC Testing for Autologous Treatments

## Autologous (Personalised Medicine)



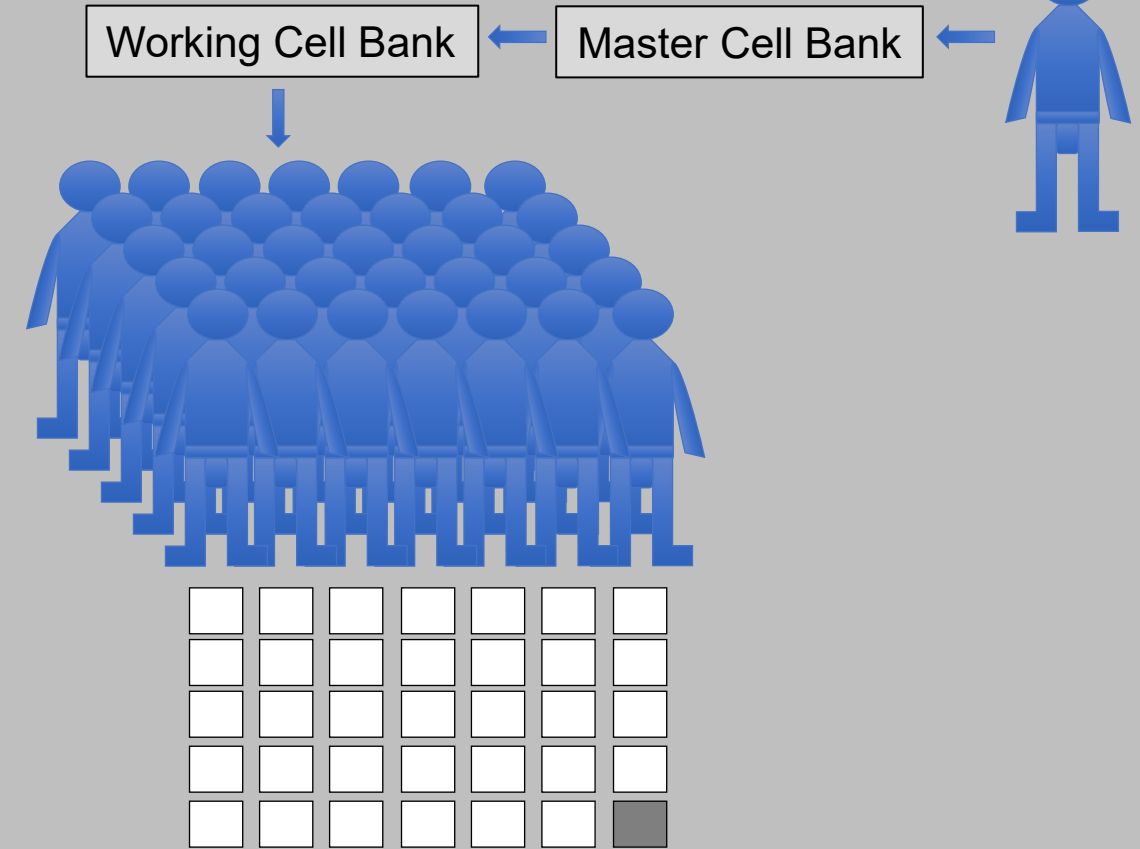
Drug product

One manufacturing run = one patient treated

QC

Higher proportion of product used

## Allogeneic (Universal “off the shelf”)



Drug product

One manufacturing run = many patients treated

QC

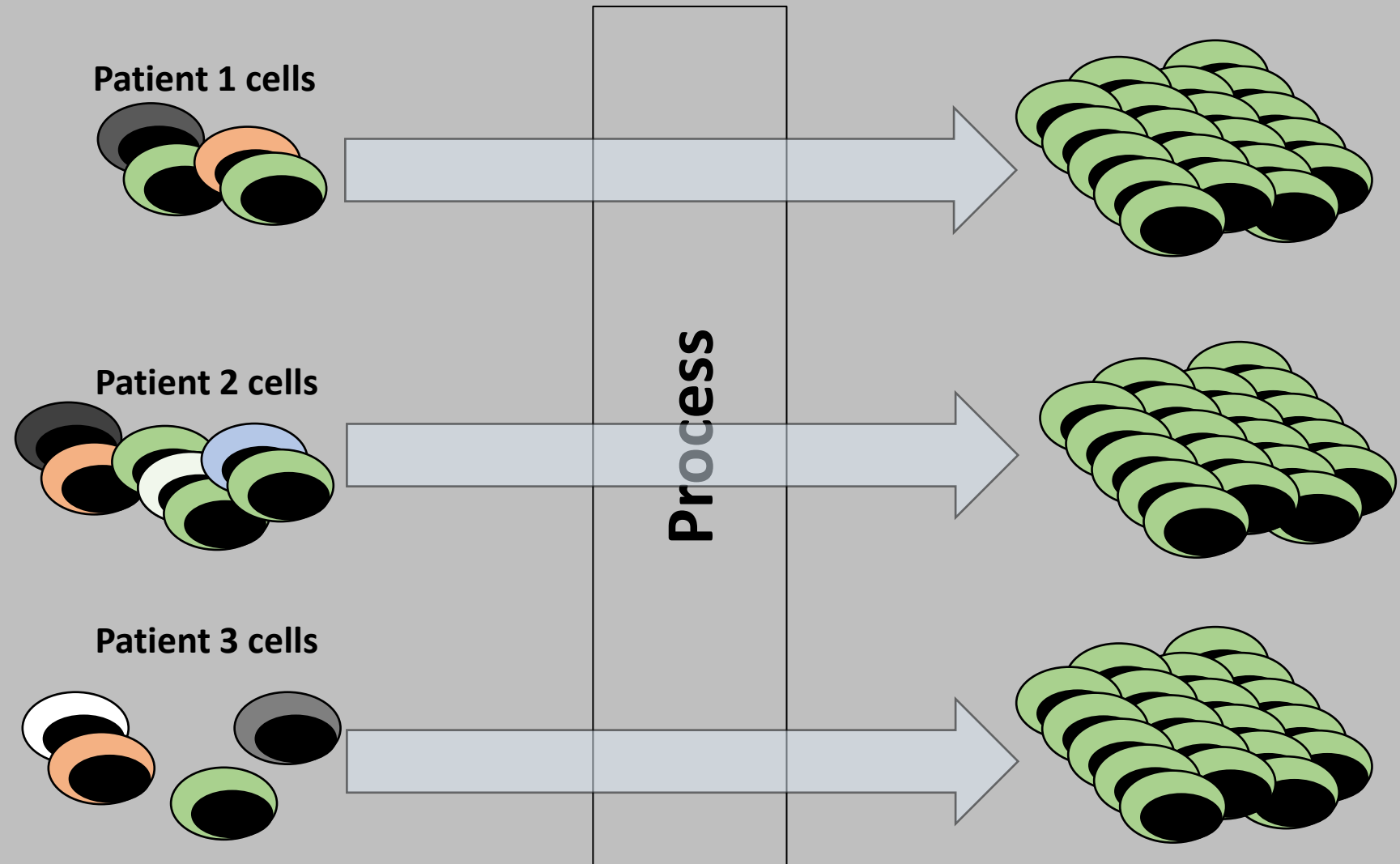
Significantly lower proportion of product used



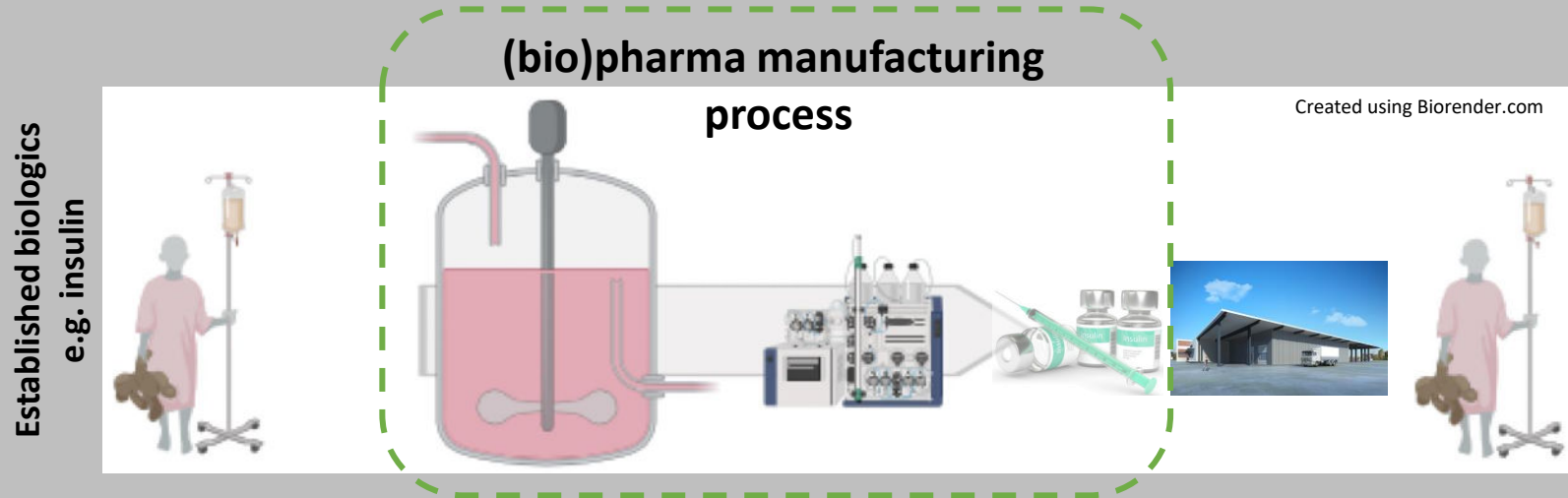
# Autologous Means Variable Start Material

**INPUT MATERIAL**

**OUTPUT DRUG PRODUCT**



# ATMP manufacture is more *involved* and risky



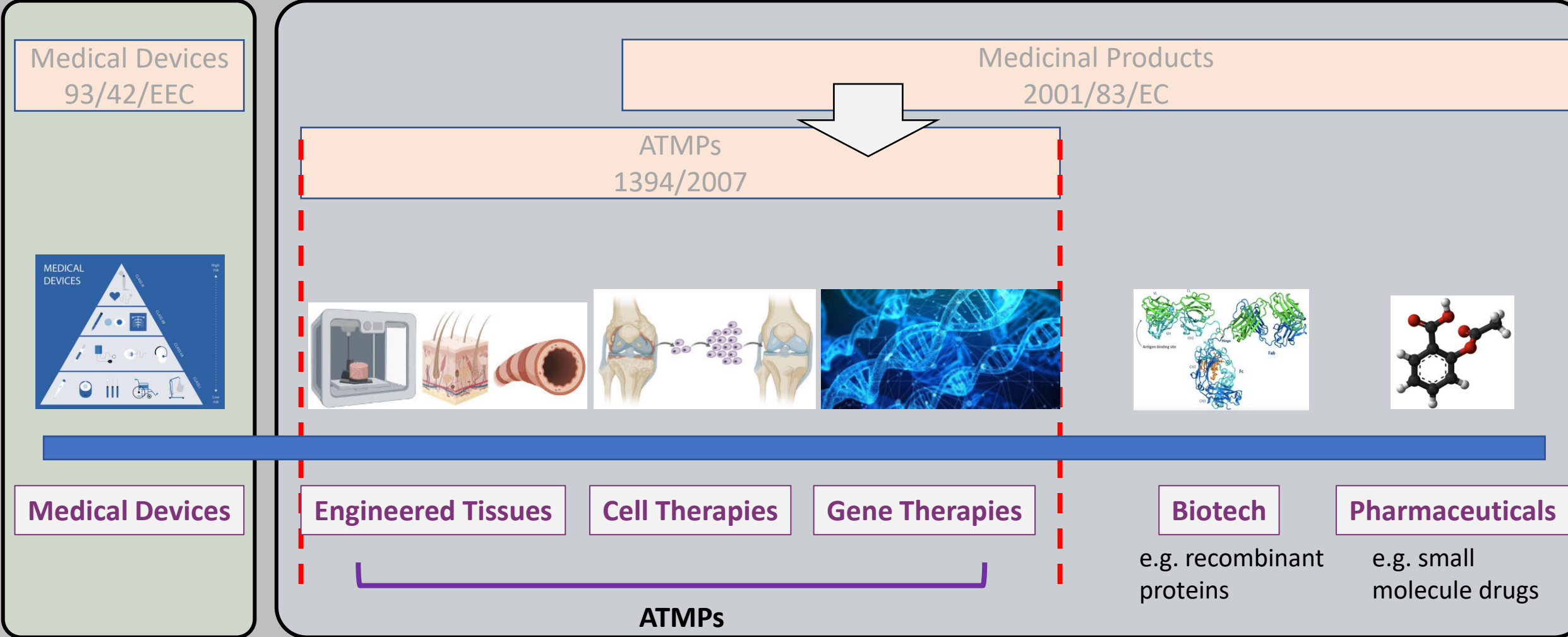
- For biologics, manufacturing is remote and separate from the patients
- A stable product is distributed



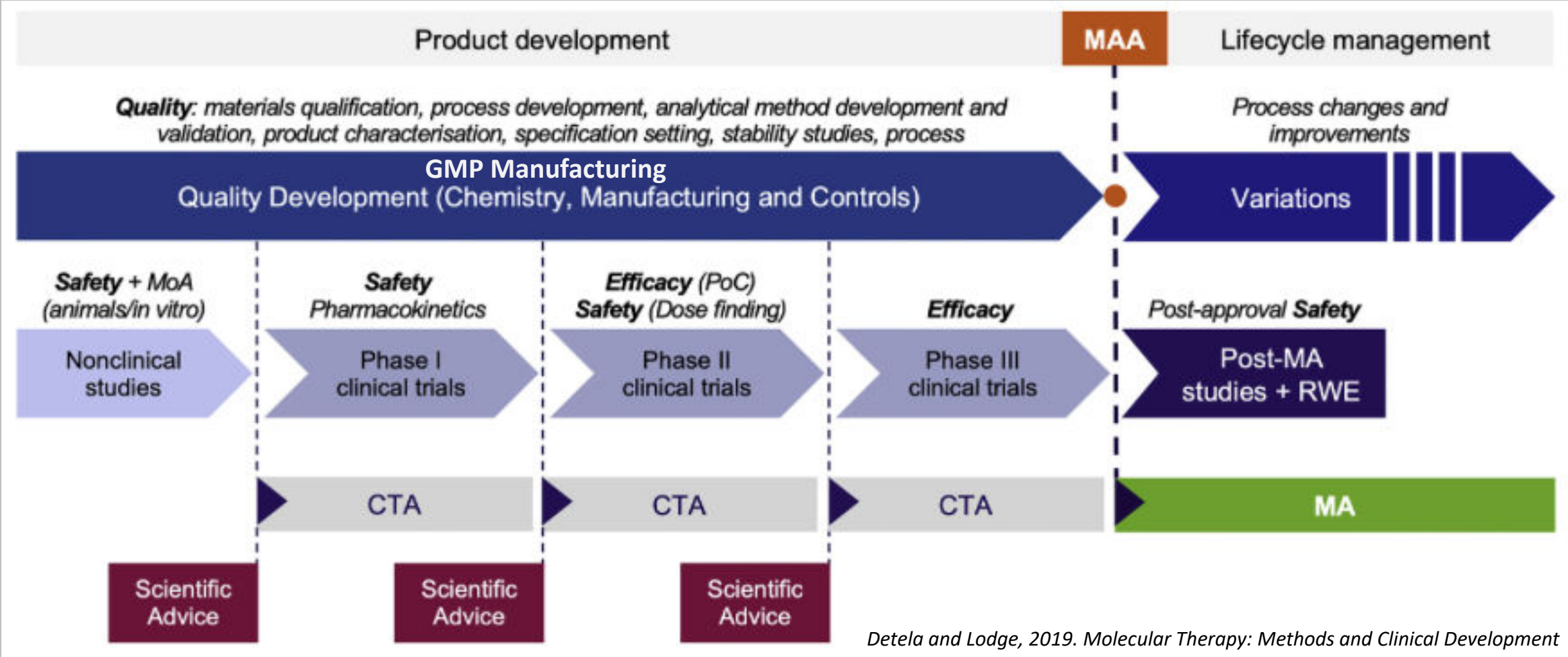
- For ATMPs, manufacturing begins at the patient's vein and ends at the patient's vein
- In between, a sequence of steps take place that result in a product that can be infused
- All along the journey, the product is "living" and responsive to environmental conditions during processing, storage and handling
- Anyone who comes into contact with the cells is part of the manufacturing process

# ATMP Manufacturing and Regulation

- Highly regulated to ensure products are safe and fit for purpose
- Relevant regulatory bodies: MHRA (UK) / EMA (EU); FDA (USA)
  - Assess and inspect the evidence for the safety and effectiveness of medicines



# Manufacturing Cell and Gene Therapies



Detela and Lodge, 2019. Molecular Therapy: Methods and Clinical Development

# GMP Manufacturing Facility



Courtesy of Prof Julie Daniels, UCL



Miltenyi Biotec



# Manufacturing Cleanroom



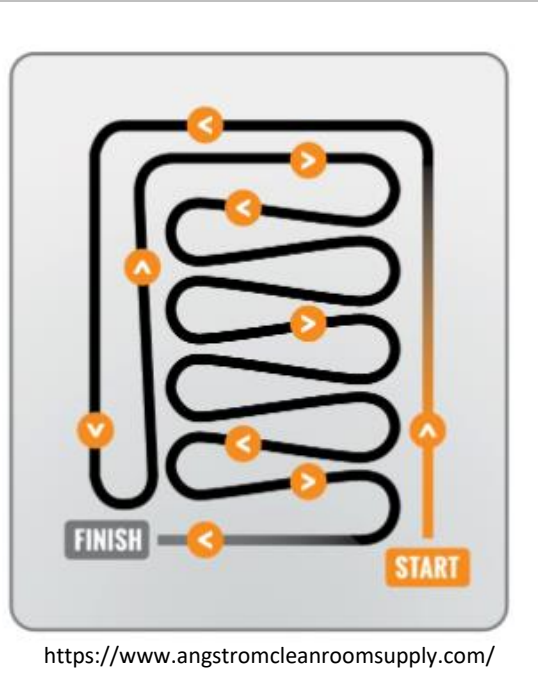
Gowning



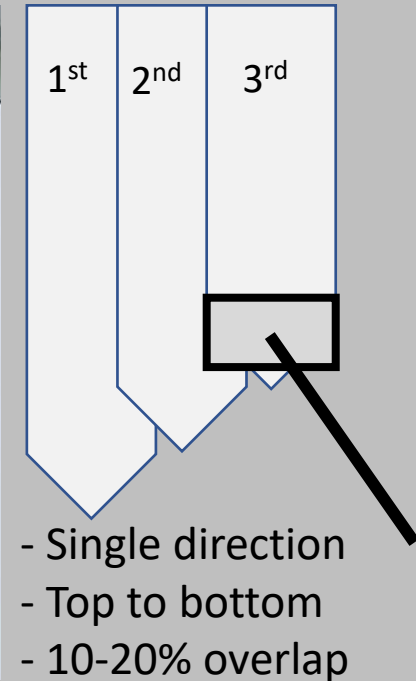
Cleaning

# Manufacturing Cleanroom

Floor mopping



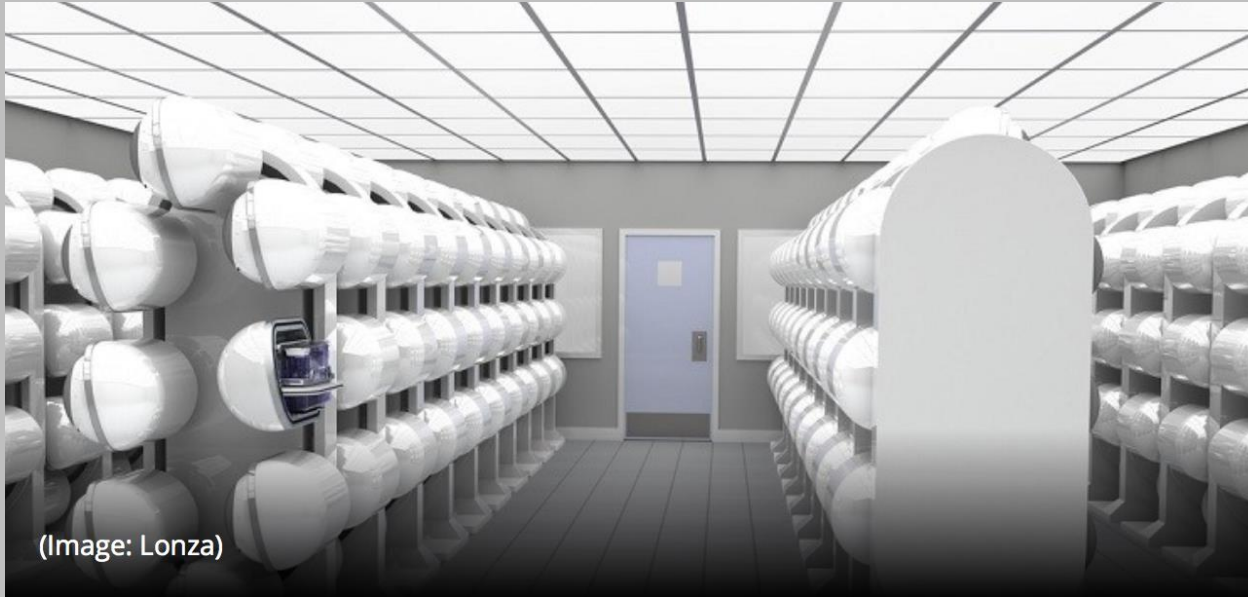
Wall mopping



- Follow the pattern and repeat every 20m<sup>2</sup>
- Overlap paths to make sure no surface area is missed
- Mop in single direction
- Work backwards pulling the mop towards you

# The Future of ATMP Manufacturing...

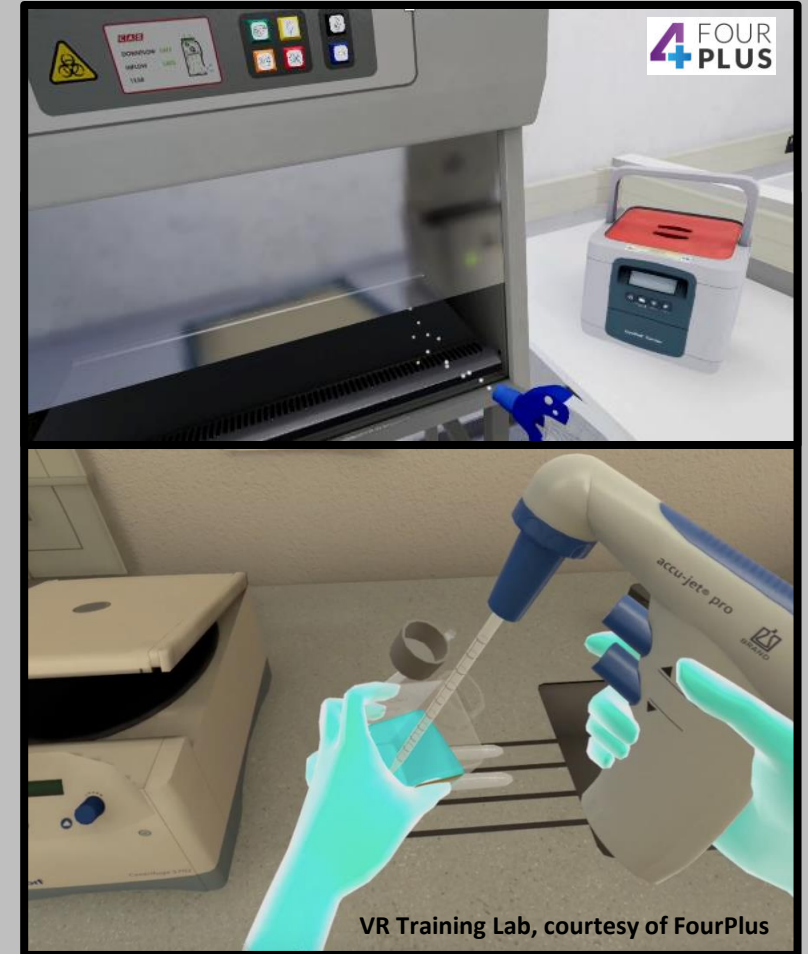
## ... is Almost Here



(Image: Lonza)

Industry Vision for Scaling “Up”

- Creation of flexible manufacturing facilities and equipment



VR Training Lab, courtesy of FourPlus

Immersive Technology for Workforce Management

Thank You for Listening

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# Q&A

- Please add any question you have into the Q&A box
- Please fill in feedback survey, your input is really valuable to us
- New series of webinars coming up starting January 2020, look out for adverts