



# Overcoming Challenges in Manufacturing Allogeneic Cell Therapies

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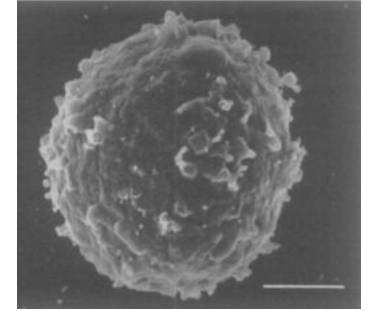
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# Topics

Allogeneic CT Manufacturing

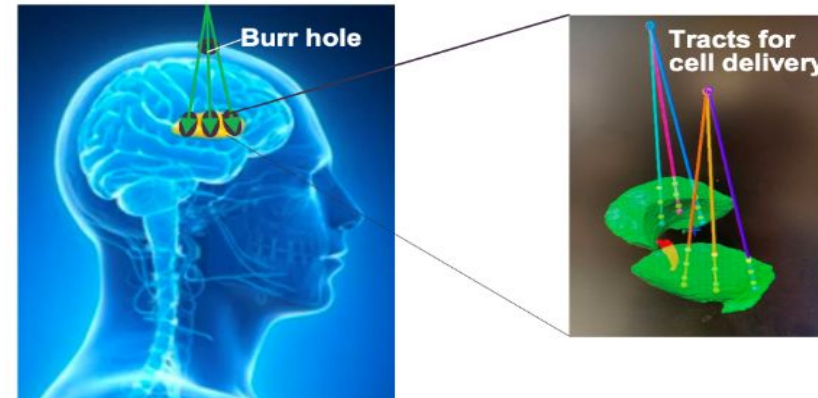
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# Parkinson Disease - Bemdaneprocel Transplantation

Making healthy dopaminergic neurons to restore brain function



- Investigational cell therapy designed to **replace the dopamine producing neurons** that are lost in Parkinson's disease
- Derived from pluripotent stem cells (PSC) that originate from human embryonic stem cells
- Bemdaneprocel is surgically implanted into the brain of a person with Parkinson's disease (Phase III started)

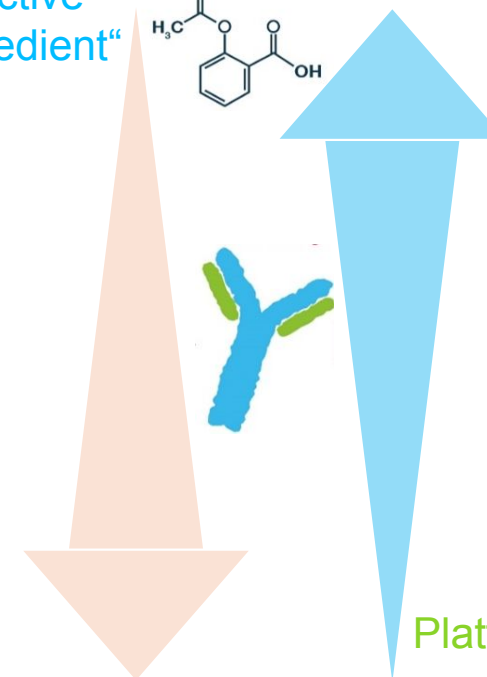
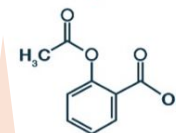


# Making Cell Therapy A Reality for Patients

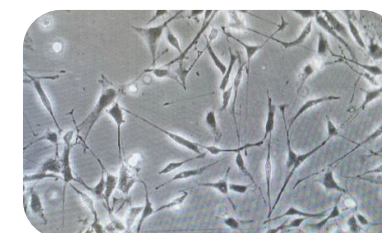
New technologies, stringent process control and consistency are of paramount importance in CT Manufacturing

- CT products are subject to evolving **Quality and Regulatory** criteria
- **Living product** is the most complex product class in manufacturing
- General **lack of platform processes and equipment for industrial scale CT**
- Any change in **process / environment** could have an impact on cells; they may slow growth, change level of a surface marker(s), genomically alter, etc.
- **Cell Care**. Cells can be sensitive to handling, materials, freezing, shear, temperature => need data from constant monitoring, esp. **real-time monitoring**
- Process **execution** is critical => a technical issue can kill a batch
- **Automation and “platformability”** would help.

Complexity of „active ingredient“



Platformability





# Our Ambition: To Become A Leader in CT Manufacturing by Creating An Innovative Modular Platform

Allogeneic CT Manufacturing

“Software” =  
CT Process Platform

“Hardware” =  
CT EQT Platform

“Operating System” =  
CMC Ecosystem

People Platform

## Target

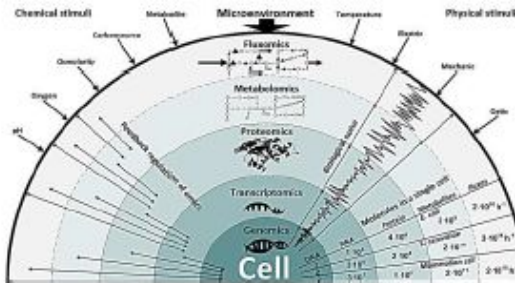


Fundamental **understanding** & **control** of **cell** systems & processes

Well- characterized, automated, robust EQT **modules tailored** to process needs

**Standard workflows** supported by **efficient, data-driven** decision making

High-performance **team**, **well connected** within and outside Bayer



## Approach

- // **Manuals for process development** for all relevant UO, based on a fundamental **process and product understanding**
- // **Small-scale models**
- // **Description** of large-scale processes

- // White paper on **equipment design and automation**
- // Engineering and automation **specifications**
- // Plug and play **pilot**

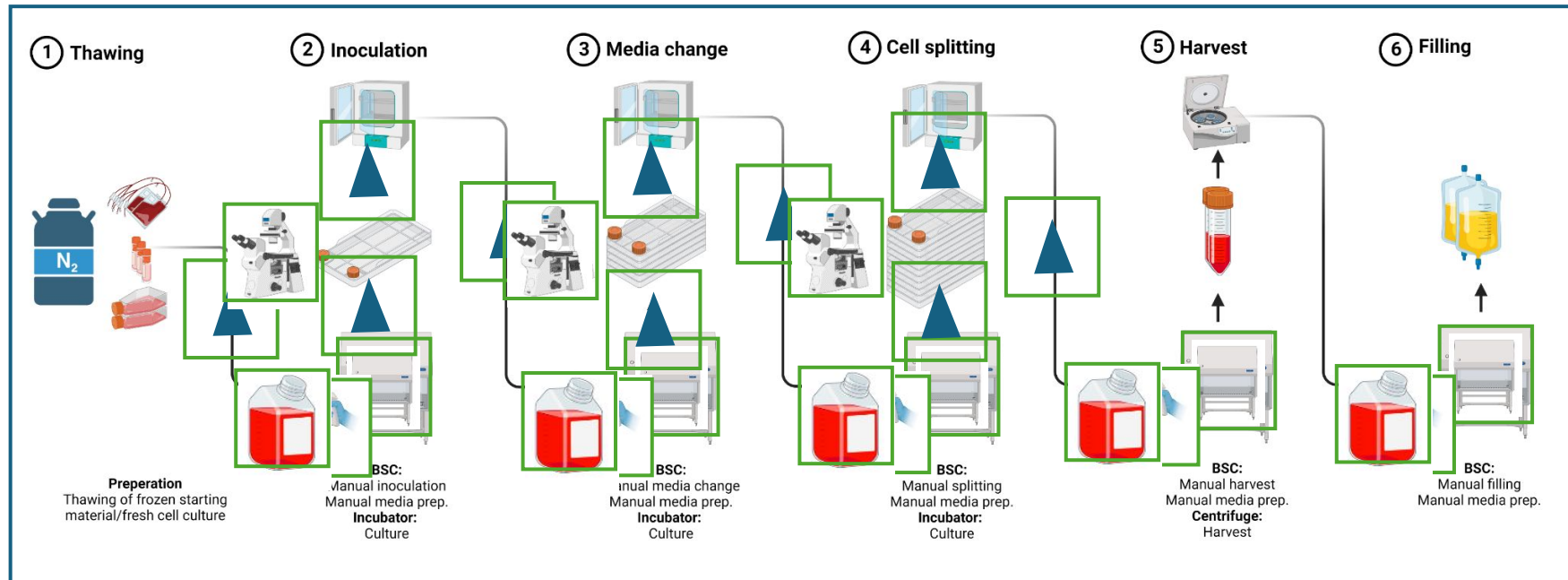
- // **Development Plan** for CT products
- // **Control strategy** for product development (QbD)
- // Phase-appropriate **filing templates**

- // Strong **CT competencies and capabilities**
- // **Agile collaboration** and **cross-group best-practice exchange**
- // Strong internal and external **partner network**



# Generic Manual Process for 2D Expansion & Differentiation

Inherent complexity in many steps over weeks to months



**1 Thawing**  
Thawing of starting material from cell bank in vial or bag






**2 Inoculation**  
Manual and open preparation of cell material in BSC including centrifugation, dilution and seeding on cell culture flask

**3 Media change**  
Transfer of cell culture flask, manual and open preparation and exchange of media in BSC

**4 Cell splitting**  
Transfer of cell culture flask, manual and open dissociation, centrifugation, dilution and seeding of cell solution

**5 Harvest**  
Transfer of cell culture flask, manual and open dissociation, centrifugation, dilution and formulation of cell solution

**6 Filling**  
Manual and open filling of material into final product/intermediate product bag for further processing

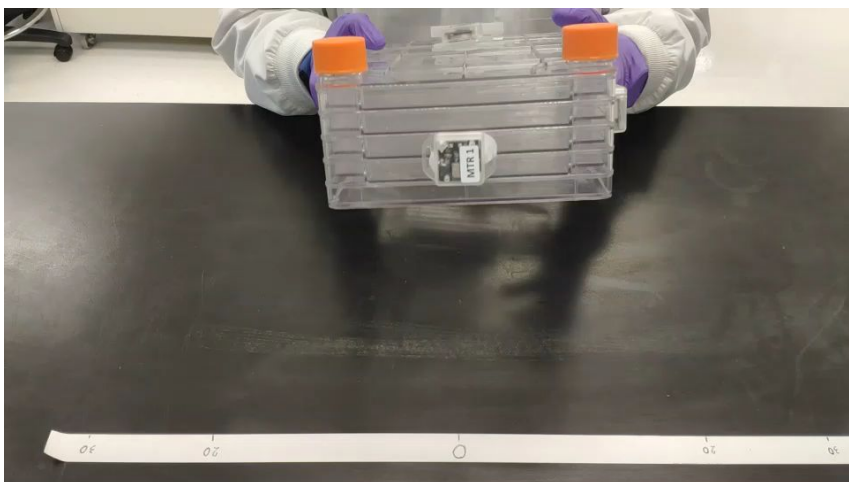
-  • Biosafety cabinet for open handling steps
-  • Manual and open media preparation
-  • Manual and open liquid handling step
-  • Culture vessel transfer
-  • Manual optical control, e.g. Confluency



# Towards Industrialization of Cell Therapy Manufacturing

## Evolution of Process Automation

### The Manual



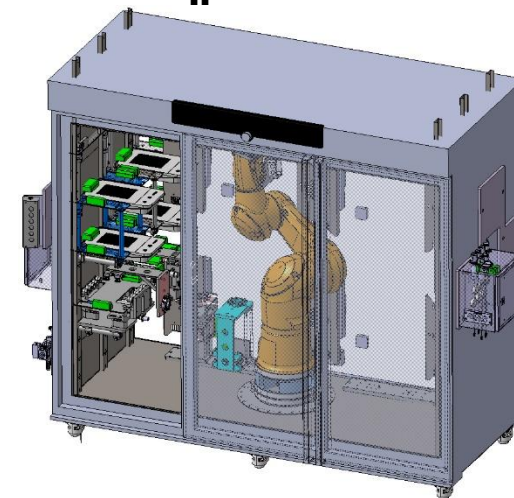
- Open handling
- Labour intensive
- Fully manual process
- Process with low reproducibility
- Changing environmental conditions

### The Present Semi-Automated



- Commercially available semi-automated equipment
- Partly open process
- Many manual steps
- Varying environmental conditions (vessel operations at ambient conditions)
- Pre-defined motions

### Tomorrow „Robotized“

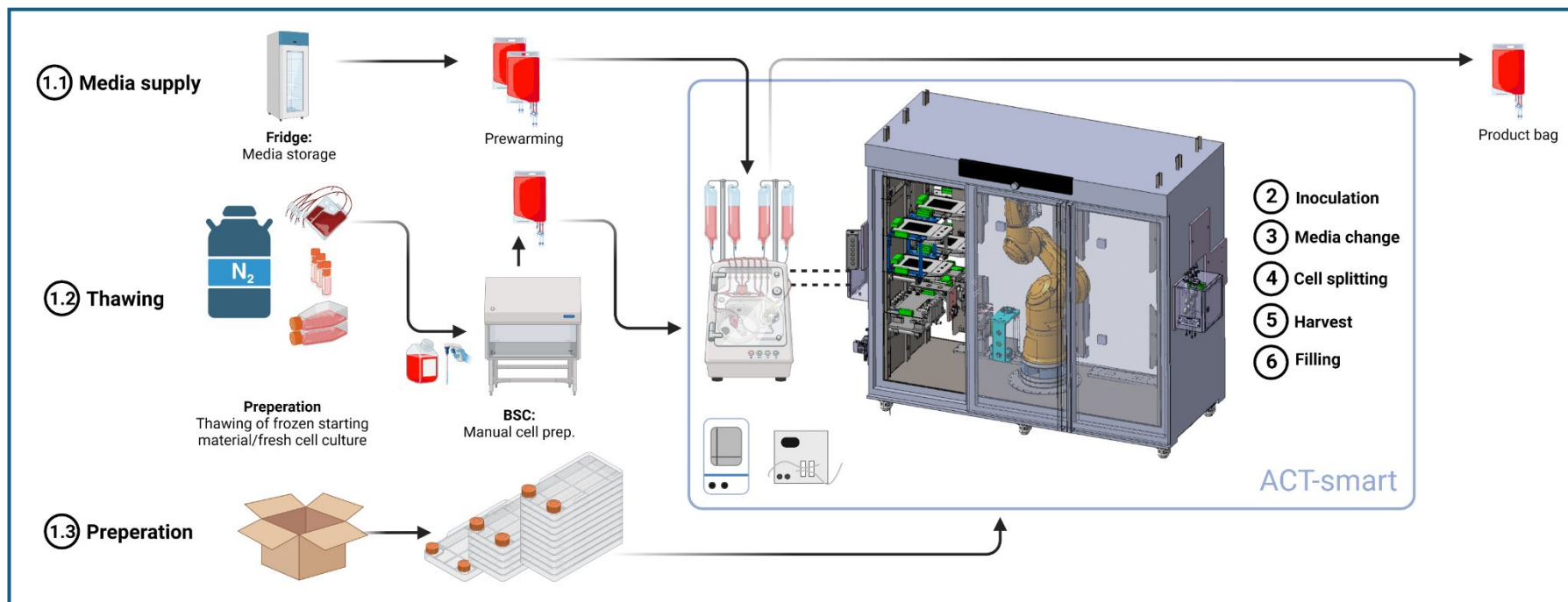








- Next generation automated equipment
- Process fully closed
- Controlled environment throughout
- Robot-controlled motions
- Digital twin of the operator
- PAT included



# ACT Smart: Adherent Cell Therapy using Smart robotics

## A Bag-2-Bag 2D Cell Cultivation System



-  • Biosafety cabinet for open handling for set-up
-  • Manual and open media preparation
-  • Manual and open liquid handling step
-  • Culture vessel transfer
-  • Automated, real-time Confluency
-  • Tube welding for closed tubing set during set-up

### 1.1 Media supply

Culture media is prepared or purchased in bags via sterile filtration and welded to the system

### 1.2 Thawing

Thawing of starting material from cell bank in vial or bag in a BSC and transfer into the inoculation bag

### 1.3 Preparation

Single use disposables and tubing set is installed and primed prior to the run

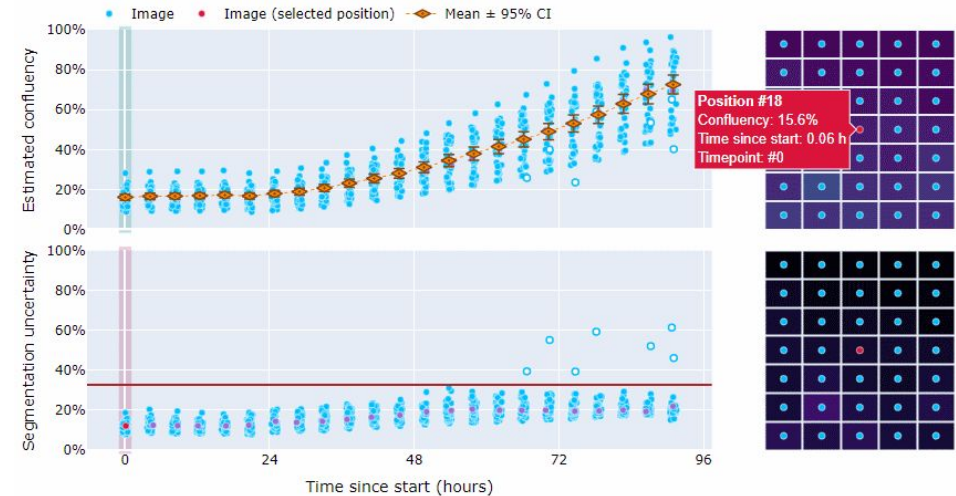
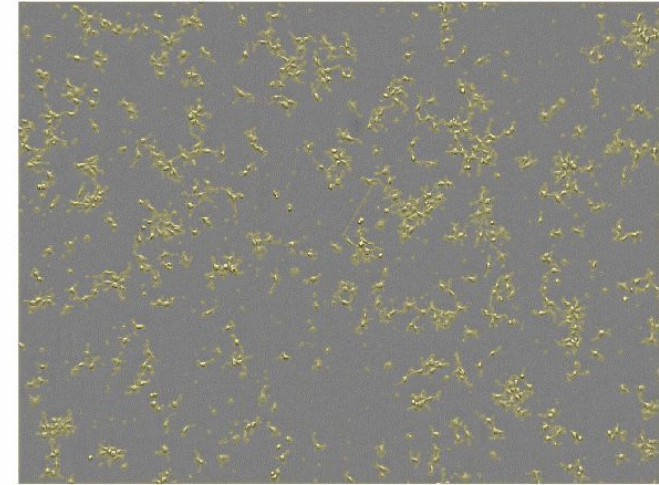
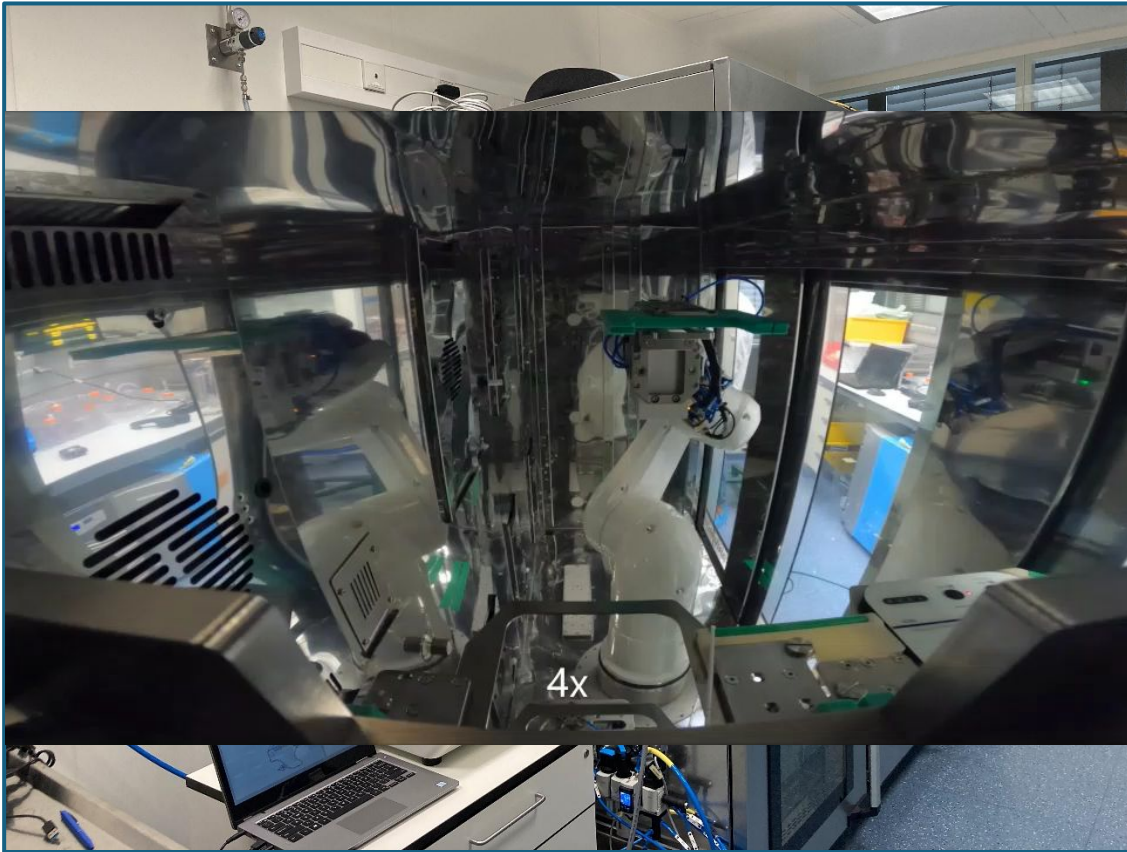
### 2-6 Cell culture

Inoculation, media change, cell splitting, harvest and filling is performed automatically using the liquid handling system for liquid transfers from and to the culture vessel, handling is performed by the robotic system. All process steps are performed inside the incubator und controlled conditions.



# ACT Smart with Real Time Monitoring

Robotic iPSC/Stem Cell Processing System with Real-Time Monitoring



Automated,

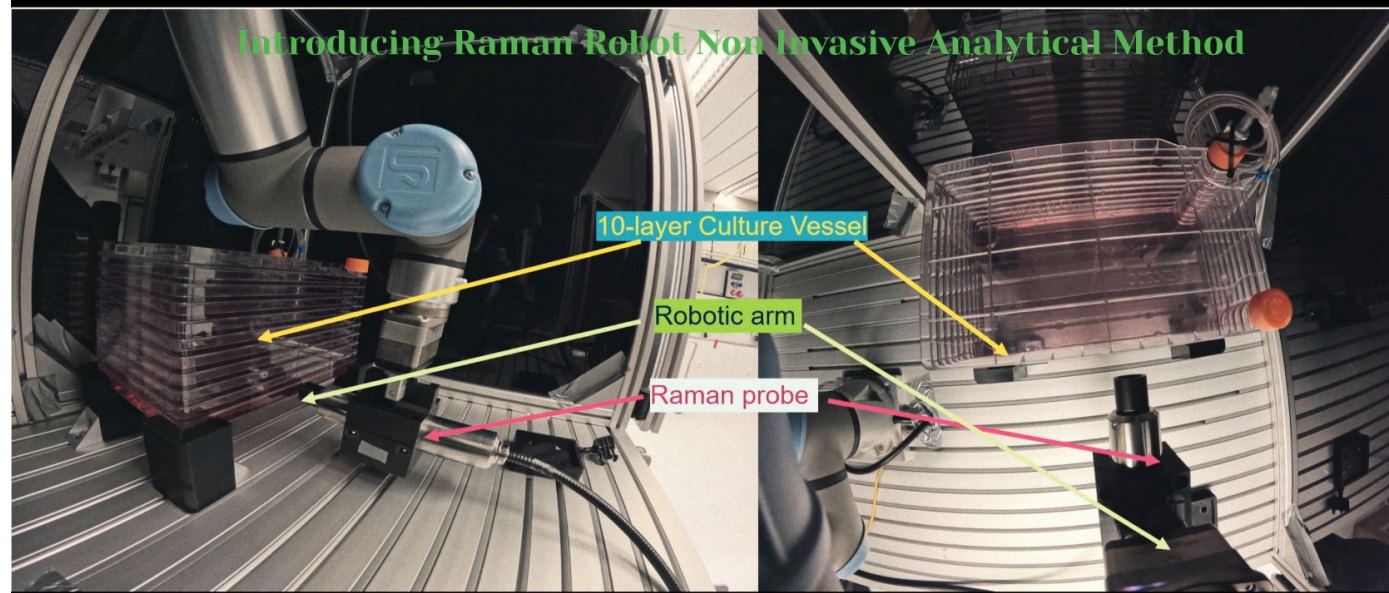
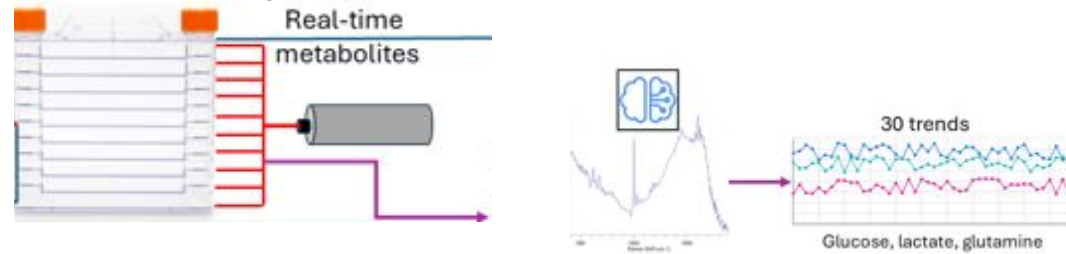
with  
Automat



# ACT Smart & Real Time Monitoring of Metabolites

Automating 2D Cultivation Systems: time resolved data for better process understanding and modeling

## Future State of Process Analysis





# F&F: Custom Building of Product Vialing at Scale

Health for all. Hunger for none

Innovative cell therapy fill & finish test lab in Wuppertal to identify cell needs & establish a Control Strategy





# Few Other Areas for Attention in Scaled CT Manufacturing

To Support Product Safety and Quality

- ✓ **Cell wash** that can reliably handle very large scale rapidly with high recovery
- ✓ Integrated **All-in-One equipment** appropriate for cells in GMP
- ✓ Other Considerations: **Step durations** that are cell-suitable, cell settling/homogeneity, visual inspection of turbid suspensions, etc.
- ✓ Cost



# Considering Long-Term Growth: Industrialization with 2D

## The Challenge

- ✓ Like manual 2D production, **automated** 2D manufacturing can take weeks to months, and has relatively large facility requirements, and costs. What is the alternative?
- ✓ Imagine going from Phase I to Commercial, annually serving 10,000 patients instead of 12:

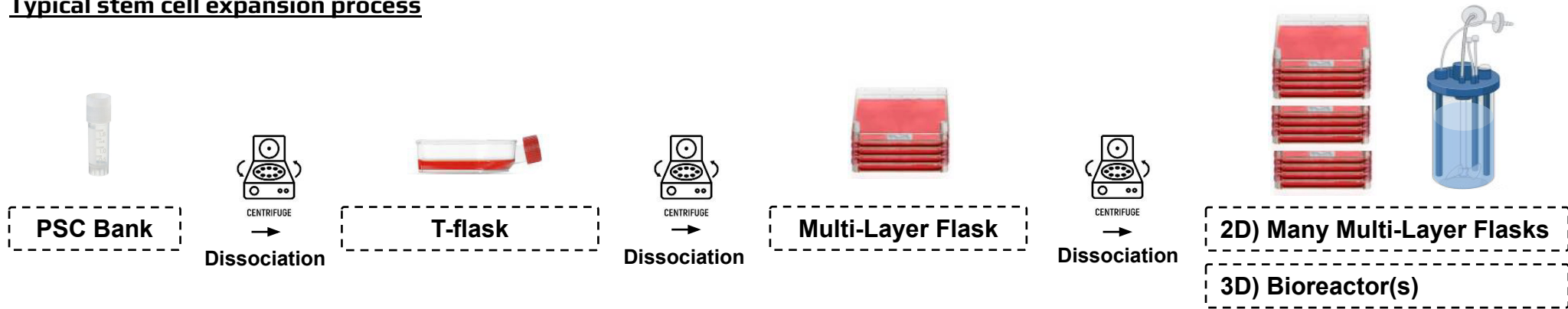
Introduction of each new equipment during scale up will require **Comparability** with GMP grade cells and equipment. Introduction of 4 technologies for scale up can occupy a manufacturing floor/facility for months to years in order to produce cells and complete Comparability at scale.

How can we further advance manufacturing in order to provide for large patient populations?  
We have been pursuing this...

# Challenges and Potential Areas of Improvement

PSC manufacturing and commercialization point of view

## Typical stem cell expansion process



- 1 Closed-System
- 2 Protection -
- 3 Scalability -
- 4 Batch-to-Batch variability, off-scale, cost
- 5 Automation -
- 6 Monitoring -

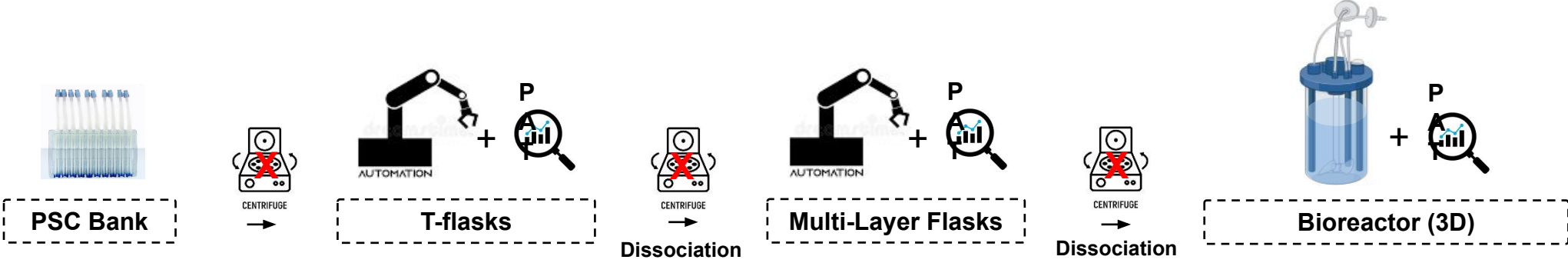


# Scalable Closed/Automated PSC Expansion Process

## Process

Addressing most of the challenges mentioned earlier

### Closed and automated stem cell expansion process



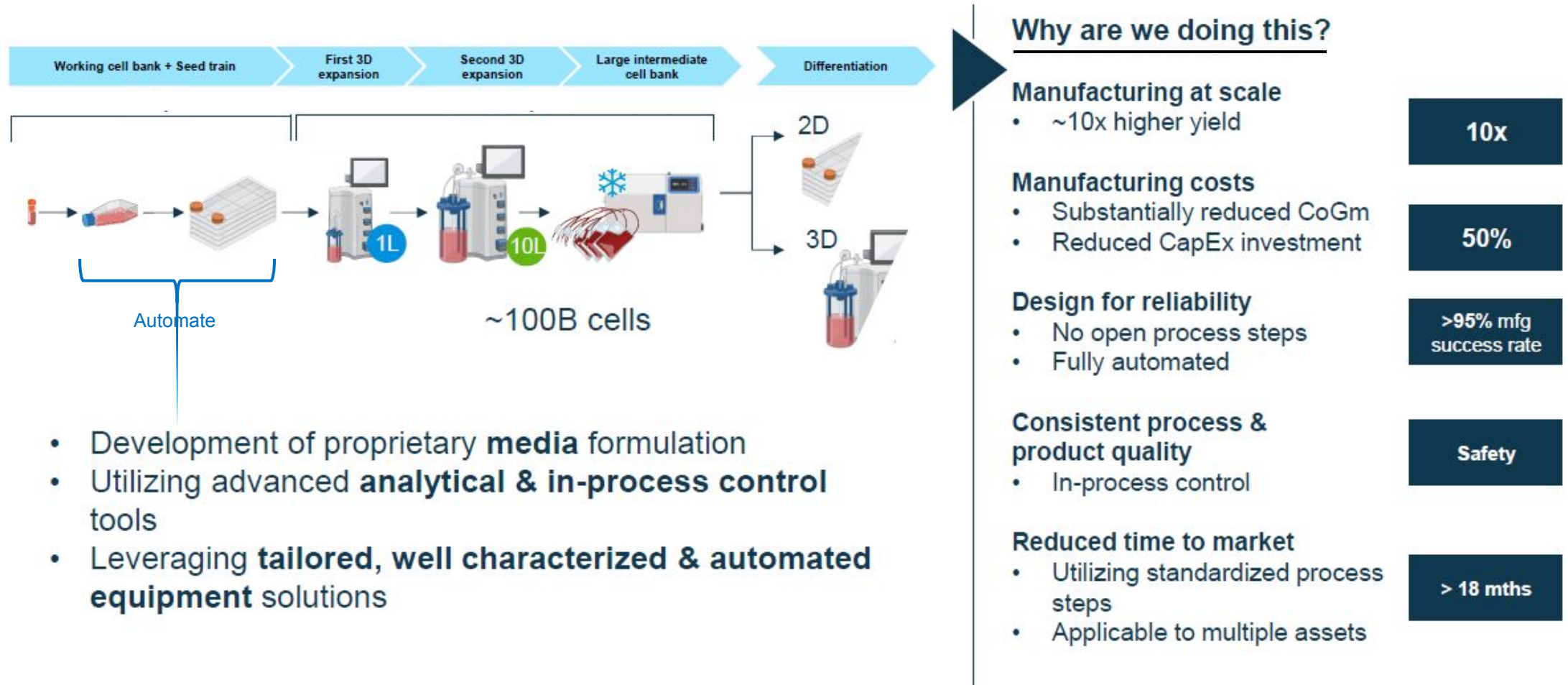
- 1 Closed & Automated
- 2 System - Scalability -
- 3 Proportion to Batch
- 4 Scalability -
- 5 Reduced from Manual
- 6 Monitoring (not required)



# Developing An Industrial Scale Cell Cultivation System

3D Cultivation

Health for all. Hunger for none



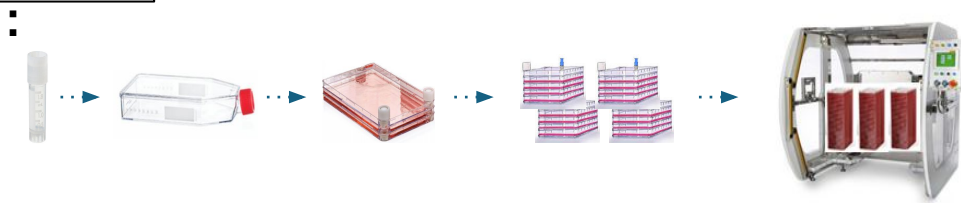
- Development of proprietary **media** formulation
- Utilizing advanced **analytical & in-process control** tools
- Leveraging **tailored, well characterized & automated equipment** solutions



# Bayer Is Advancing Manufacturing of PSCs for Large Patient Populations

Overcoming issues in yield, cost and consistency to make quality products

From



To



Bag Thaw



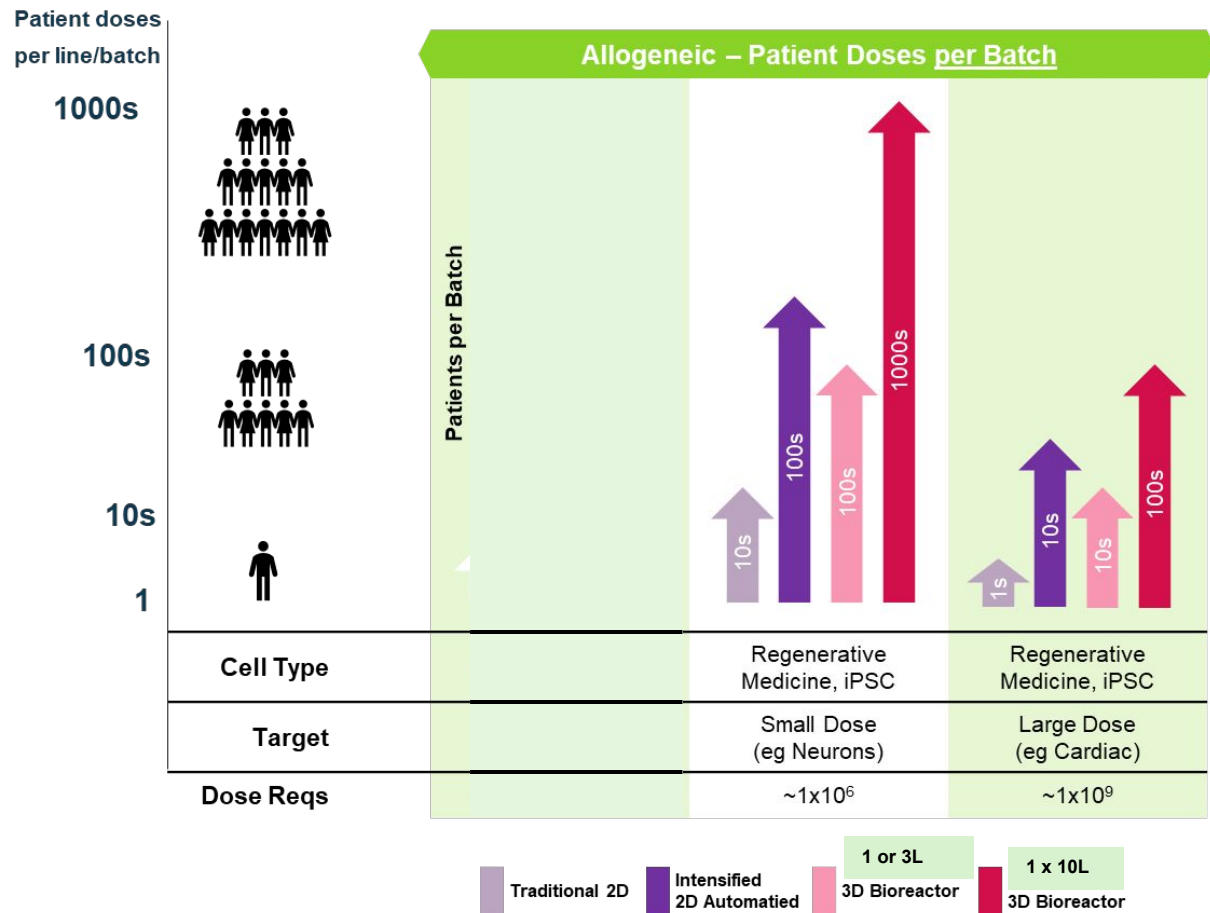
Expansion in a  
10L Bioreactor  
→ 100B PSC

**PSC differentiation** in bioreactors has been successfully demonstrated and is also in development



# What's Next?

End-to-end industrialization platform for allogeneic cell therapies will bring promise to thousands of patients



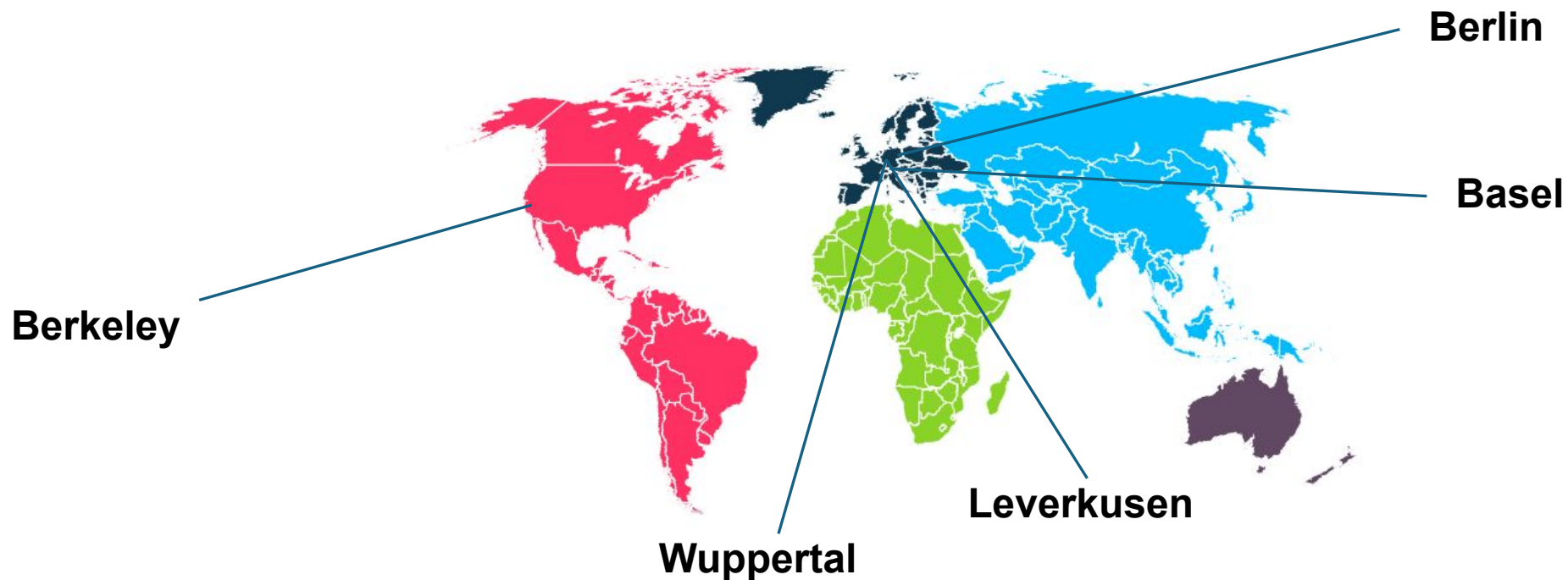
**Berkeley Allogeneic Facility (FOYA 2025)**  
 will be able to serve  
**10,000 – 100,000s patients annually**

# Bayer Contributors to Next Gen Processes

Health for all, Hunger for none



Thank you to colleagues across Bayer sites



Health for all, Hunger for none



Thank  
you!

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