



“Building the plane while flying it: Scaling autologous cell therapy

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MEASUREMENT CHALLENGES FOR CAR-T BIOMANUFACTURING

Imagination at work



Translational Research

- Mentor driven learning
- Deep workflow understanding
- Self-sufficiency - FIO
- Foster creativity
- Collaborate
- Share results through publication



The Young Apprentice, Stanhope Alexander Forbes





Scale Manufacturing

Industrial cGMP manufacturing is based on Scientific Management

- ~~Deep workflow understanding~~
- ~~Self-sufficiency - FIO~~
- ~~Foster creativity~~
- ~~Share results through publication~~
- Process measurement and management
- Attention to detail
- Process excellence is separate from manufacturing



Frederick Winslow Taylor
(1856 - 1915)



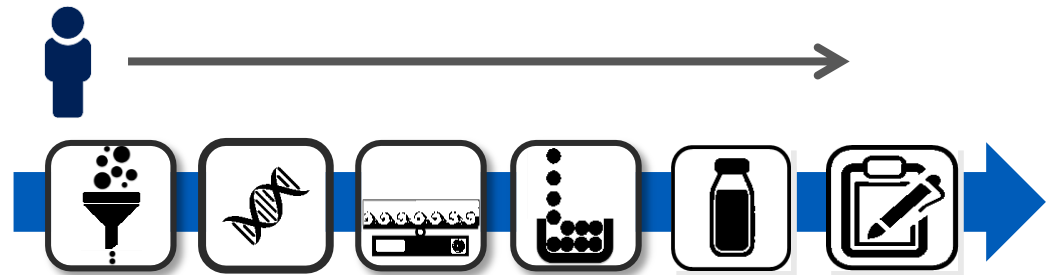
"[A laborer] shall be so stupid and so phlegmatic that he more nearly resembles in his mental make-up the ox than any other type...he is so stupid that the word "percentage" has no meaning to him..."



Process development requires deep process understanding and control

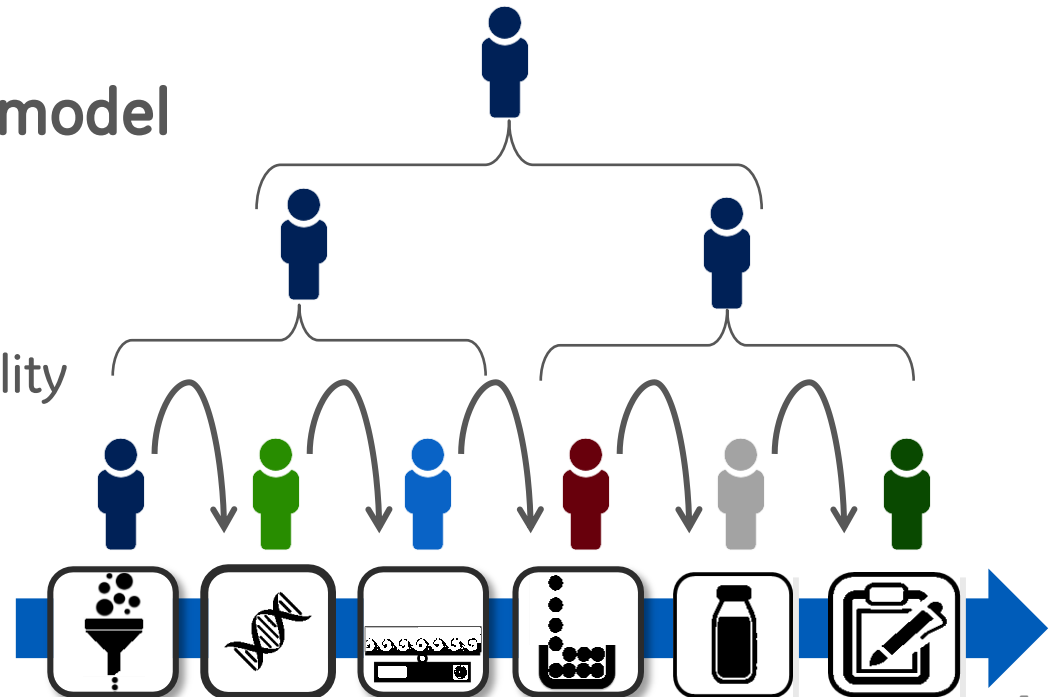
“Apprentice” model

- Process expertise
- Cell “look and feel”
- Focus on efficacy and safety



“Scientific Management” model

- Managed processes
- Sample measurement
- Lean & Six Sigma reproducibility
- Focus on productivity & risk

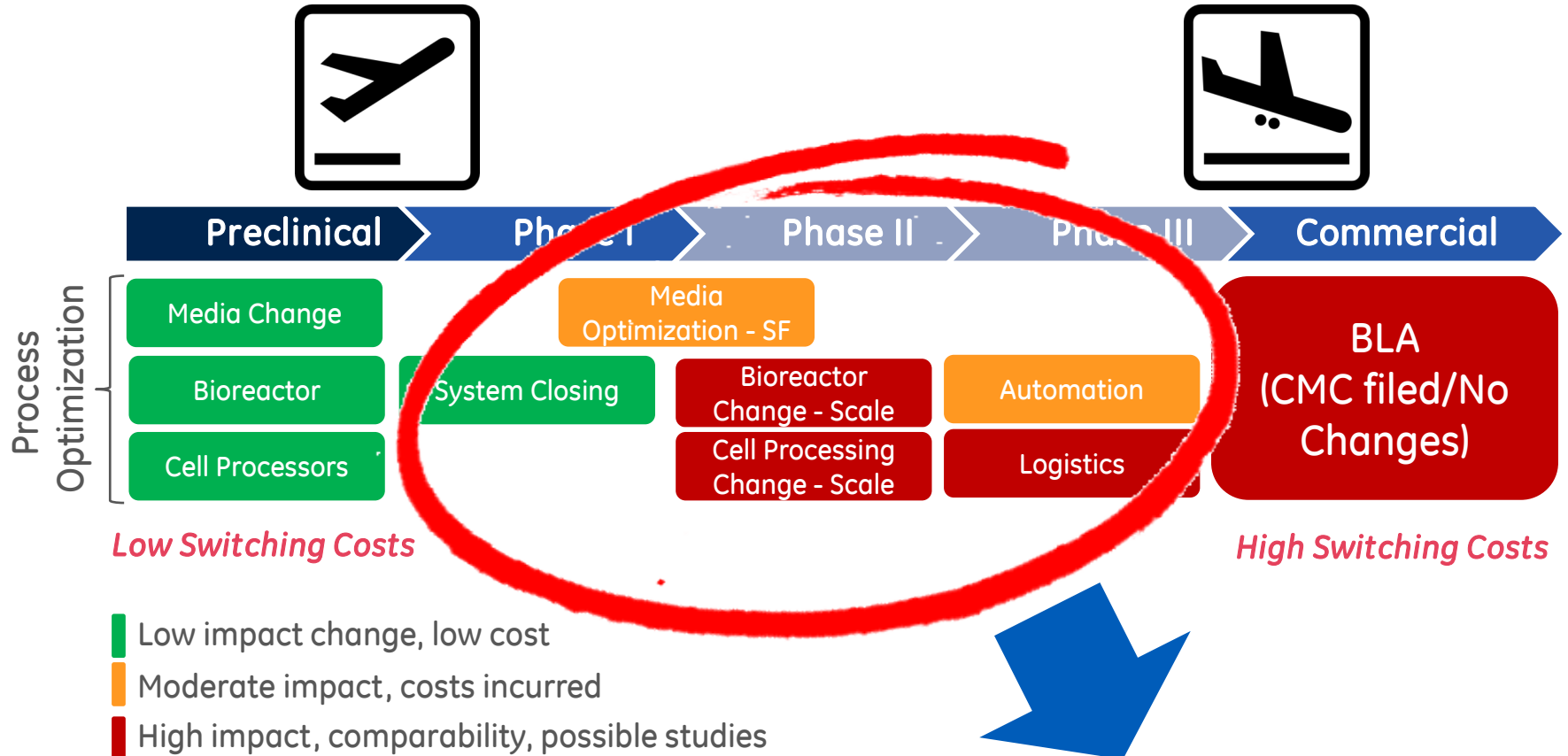


You can't manage
what you can't **measure**

Peter Drucker



Commercialization requires process control and measurement




Do these changes matter?

How far away are we?

Generic Workflow



- Repurposing bioprocess tools, blood processing tools, and/or basic research platforms
- Complex non-turnkey systems, limited standardization
- Poor interconnectivity of workflow components
- Poor IT connectivity across workflow
- Scalability → regulatory implications
- Etc.



Scale
manufacturing
process in a
controlled way for
large patient
populations

Industry is actively working towards solving these problems



New systems are being designed to derisk process and provide closed, in process monitoring



Expansion



Harvesting

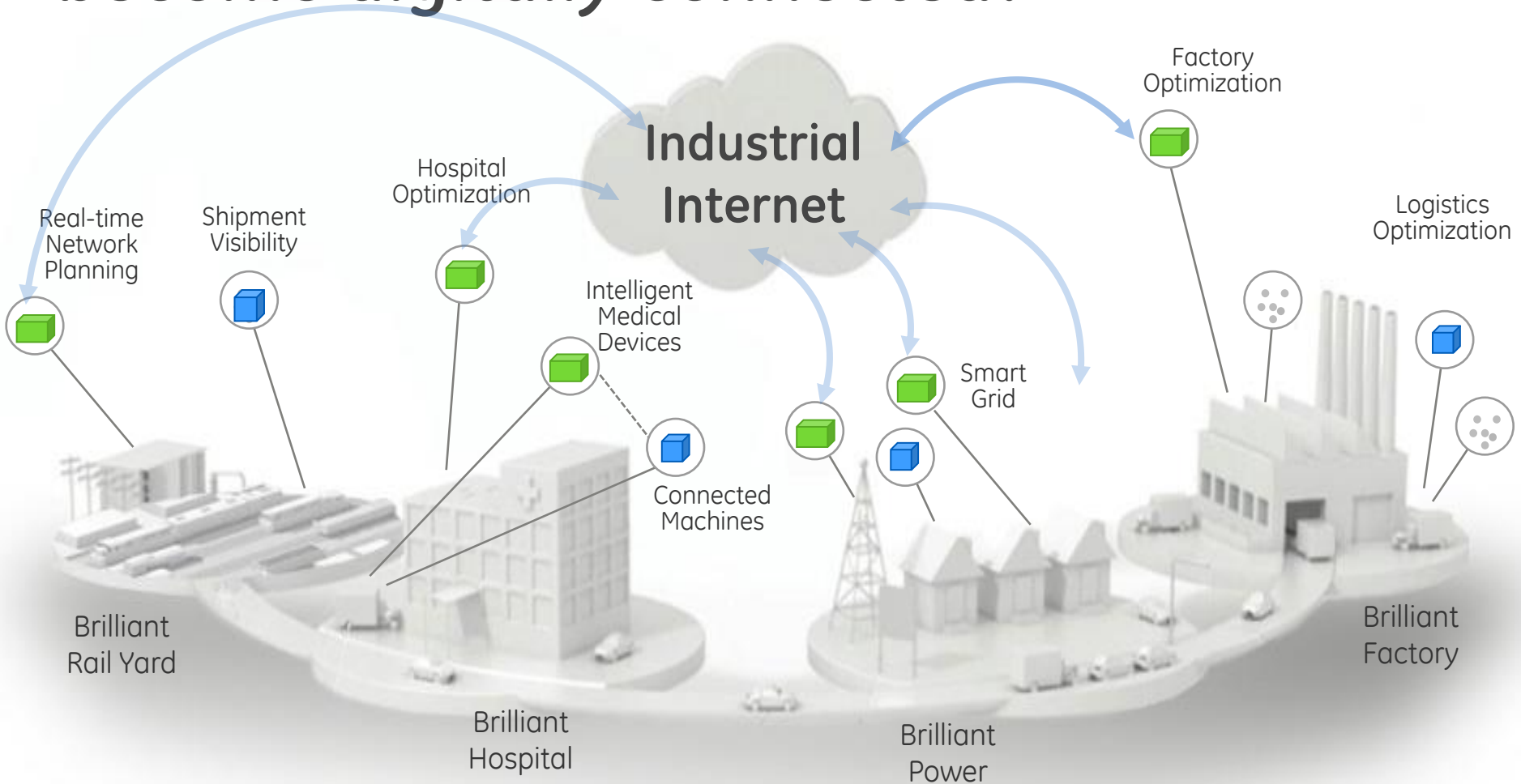


Fill & Finish



- Single use
- Disposable
- Remotely monitored
- Continuous feed
- Temp and environmental control
- Sensor enabled

What happens when 50B Machines become digitally connected?



OT is virtualized Analytics become predictive Employees increase productivity

Machines are self healing & automated Monitoring and maintenance is mobilized



Application 1: *In silico* process learning and monitoring

1 Ask the Question(s)

What are the required resources to process X patient samples per year that meet specified targets (cycle time)?

2 Process Modeling

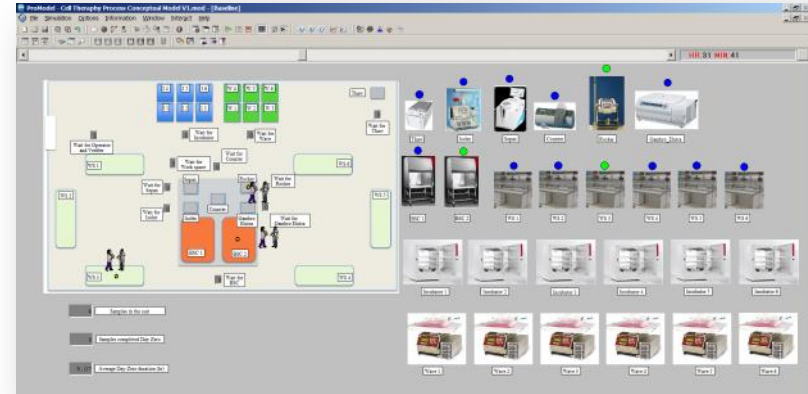
Generic T-Cell Therapy Workflow



Key Assumptions:

- Process steps, resource requirements and task cycle times are defined
- # of samples per day, per week, per year
- Define constraint(s)
- Daily shifts are defined for the Operators and Verifiers
- Task times have no variability
- Etc.

3 Run Model



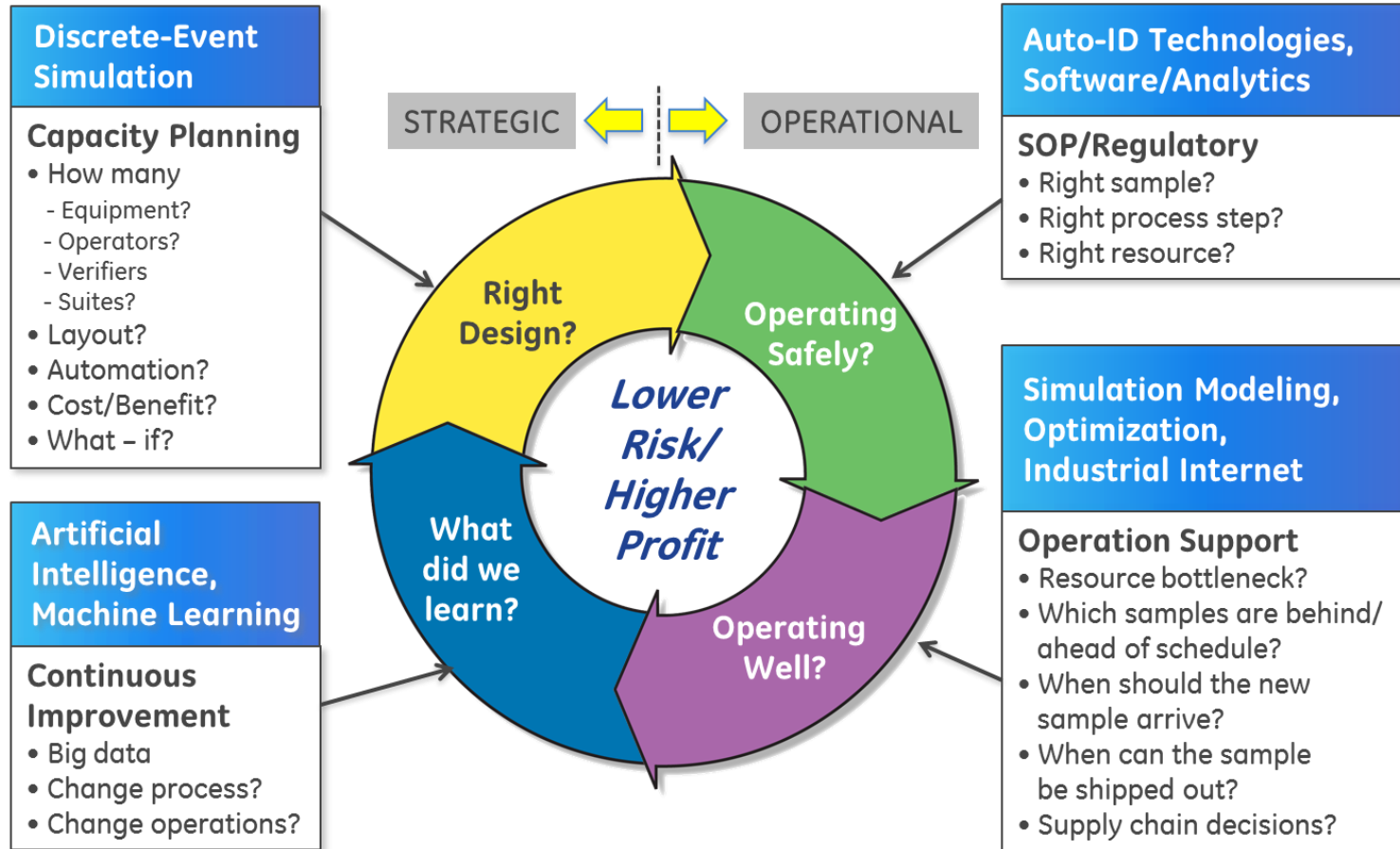
4 Analyze Results

5 Decision

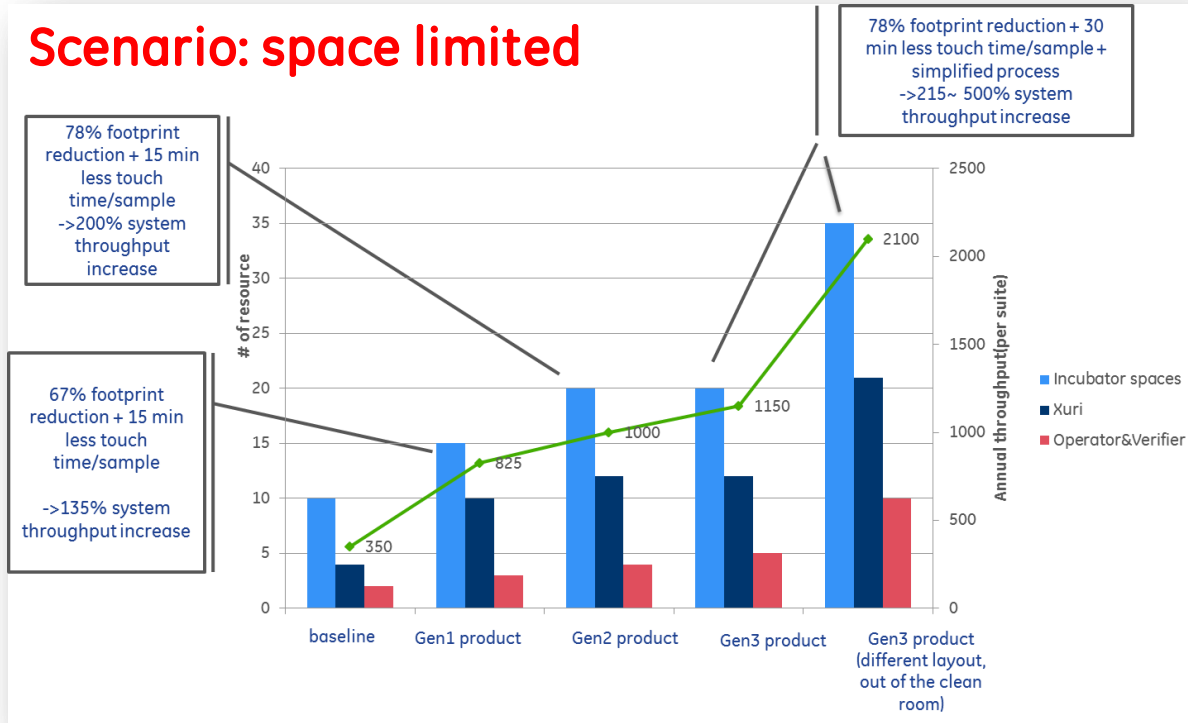
Iterate



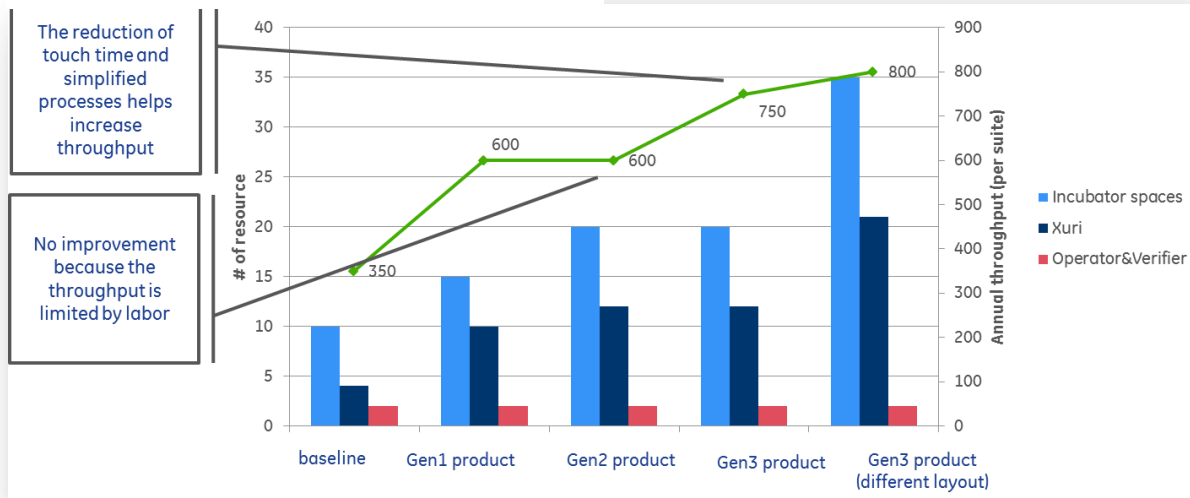
Simulation: practically applied



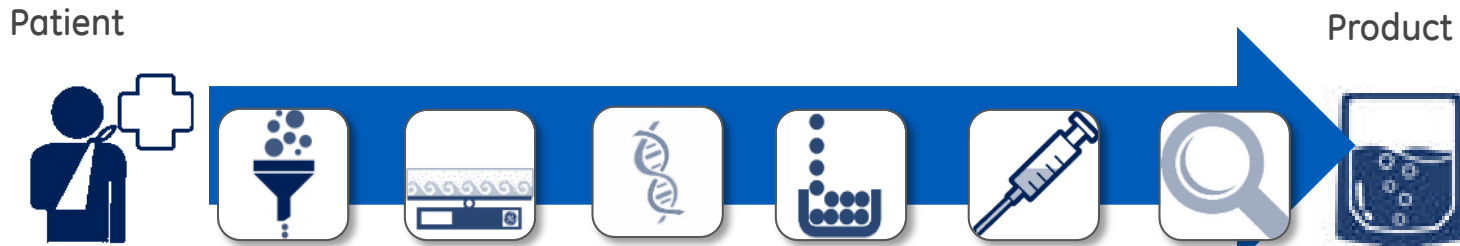
Scenario: space limited



Scenario: labor limited



Application 2: Process analytics in the cell therapy workflow

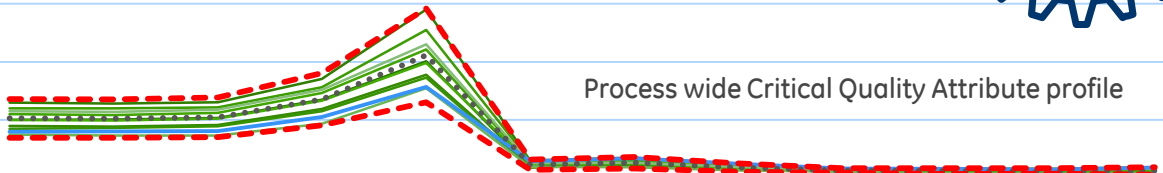


Process Subsystem Process Subsystem Process Subsystem Process Subsystem Process Subsystem Process Subsystem

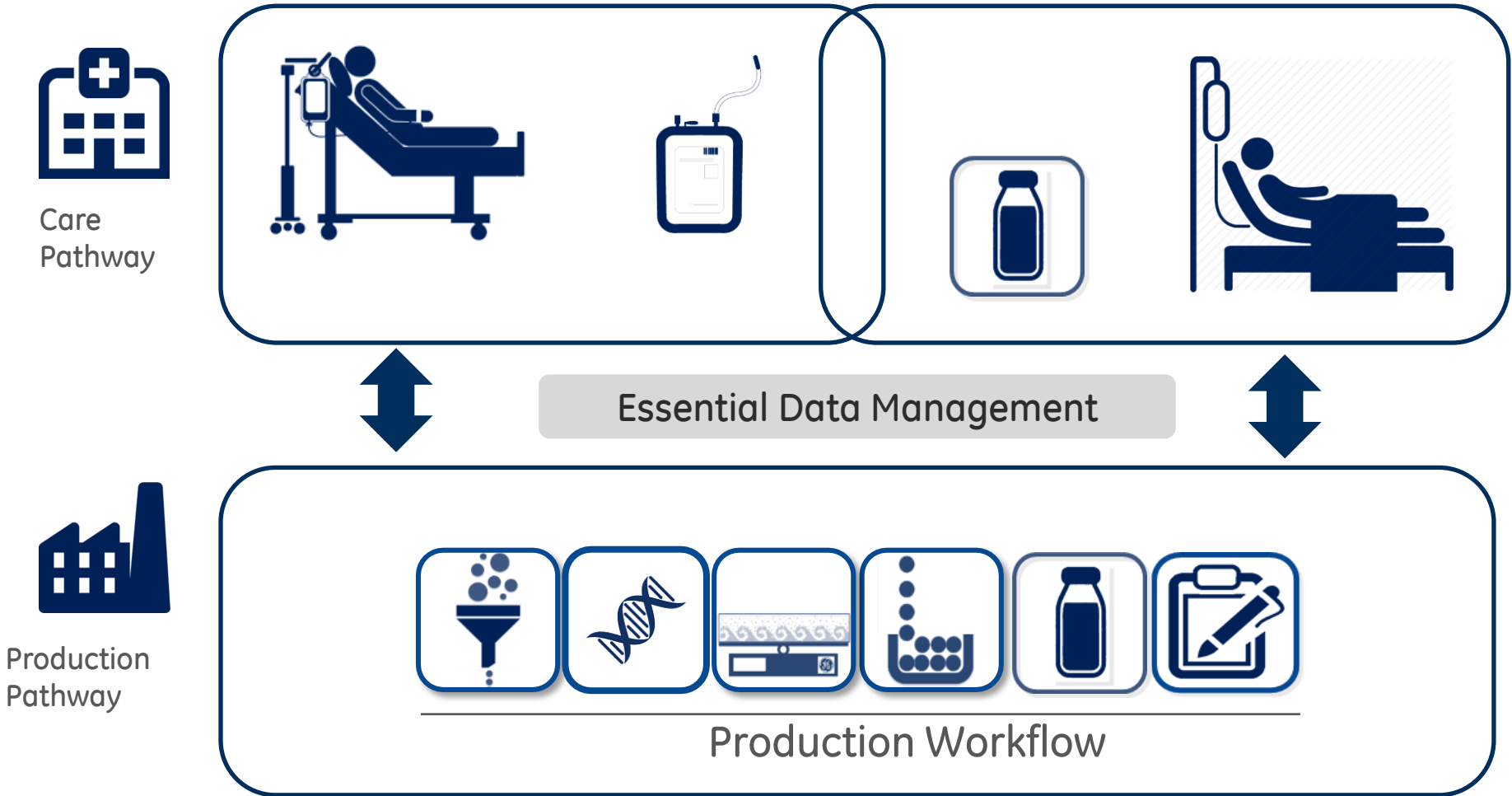
Smart Bioprocessing Analytics subsystem(s)



- HW & SW agnostic connectivity
- Context aware data aggregation and feature extraction
- Unit operation analytics based on domain expertise
- Industrial Data Lake for Big Data storage
- Process wide Big Data analytics



Application 3: Patient specific cell therapy – alignment of care and production pathways



Bridge@CCRM, a \$40 mio CAD investment to improve cell therapy manufacturing



- Technologies custom designed for cell therapy manufacturing
- Closed, disposable platforms
- Simple operation for manufacturing environment
- Flexible volumes
- Fully configurable for process development



- Connectivity of unit operations through closed "liquid circuitry"
- Process sensing and automation
- Predictive modeling and capacity planning
- Infrastructure development and implementation



- Driving collaboration across the industry
- Enabling efficient manufacturing workflows
- Connecting manufacturing and care pathways
- Solving complex problems in partnership
- Evolving new technology platforms

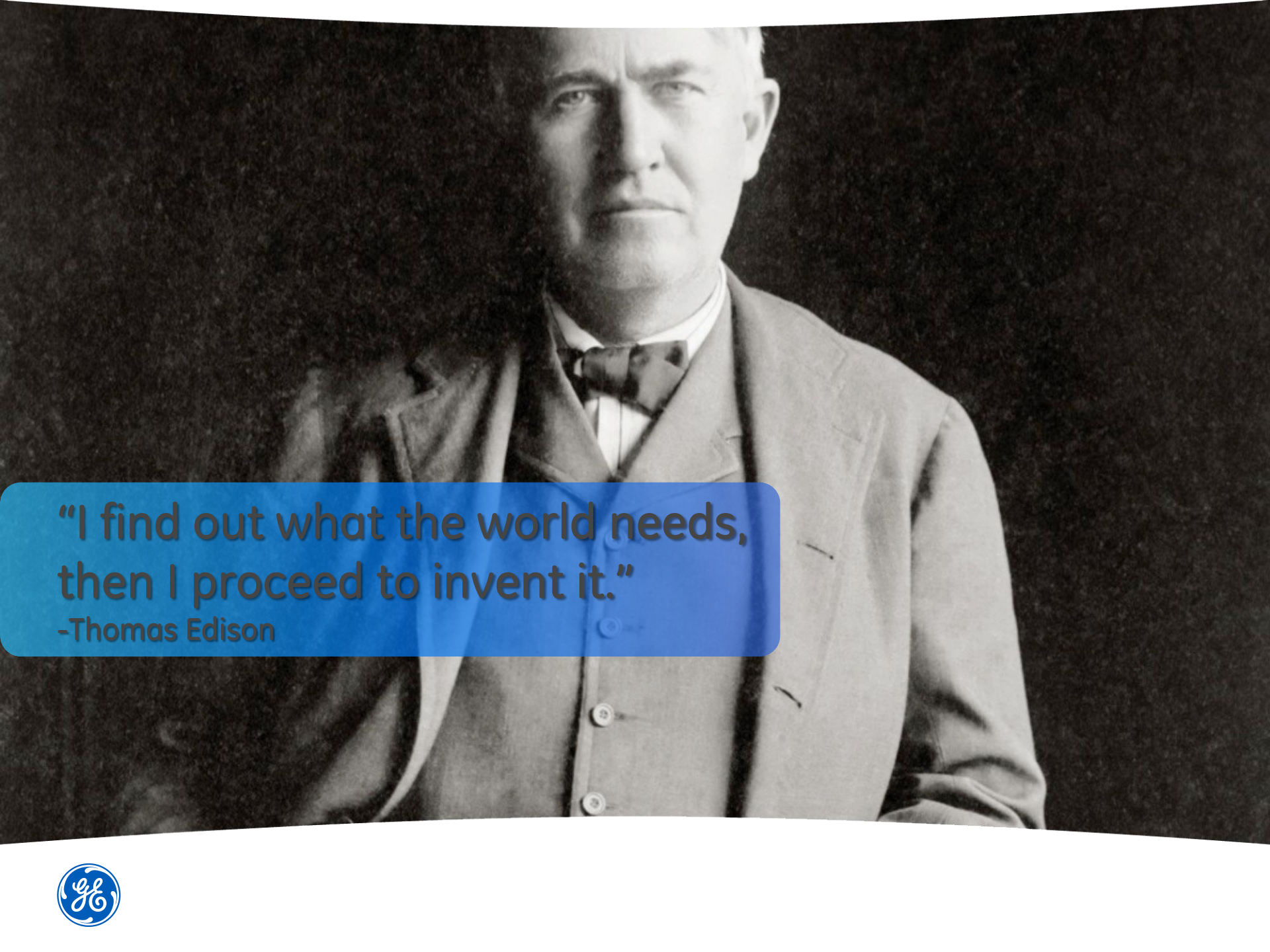
Enabling a cell therapy industrial ecosystem



Summary

- Clinical development and industrialization is occurring in lock-step but have very different metrics
 - Desperate need for process development understanding
 - Improved process measurement and management
- Process risk can be minimized by:
 - Simplifying processes
 - Designing new unit operations
 - Connecting
 - Digitizing
- Digital integration can be a powerful tool for process and facility design and optimization
- Smart analytics will lead to better and safer medicines
- Autologous cell therapy manufacturing and care pathways are converging



A black and white portrait of Thomas Edison, an elderly man with white hair, wearing a suit and a bow tie. He is looking directly at the camera with a serious expression. The background is dark and textured.

**“I find out what the world needs,
then I proceed to invent it.”**

-Thomas Edison

