Design of Quality Systems and Oversight for CGT Products under DM/POC Manufacturing Models

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- BioFabUSA is a Manufacturing USA institute
  - DoD funding
  - 175+ members nationwide

Mission: Make practical the scalable, consistent, cost-effective manufacturing of cells, tissues and organs

Technical Roadmapping Exercises

-Funding gap-filling technical projects

-Prototyping innovative manufacturing solutions

Facilitating the growth of the emerging regenerative medicine industry

Distributed Manufacturing (DM)

- A decentralized manufacturing strategy consisting of a manufacturing platform comprising manufacturing units deployed to multiple locations. Possible use scenarios include:
  - Units located within manufacturing facilities operating within the host's pharmaceutical quality system (PQS).
  - Units manufactured and installed to the same specifications at multiple manufacturing facilities, networked and operated by a central remote PQS.
  - Units as independent manufacturing facilities, each with its own PQS.

Source: "Distributed Manufacturing and Point-of-Care Manufacturing of Drugs", FDA/CDER 10/22

Point-of-Care Manufacturing (POC)

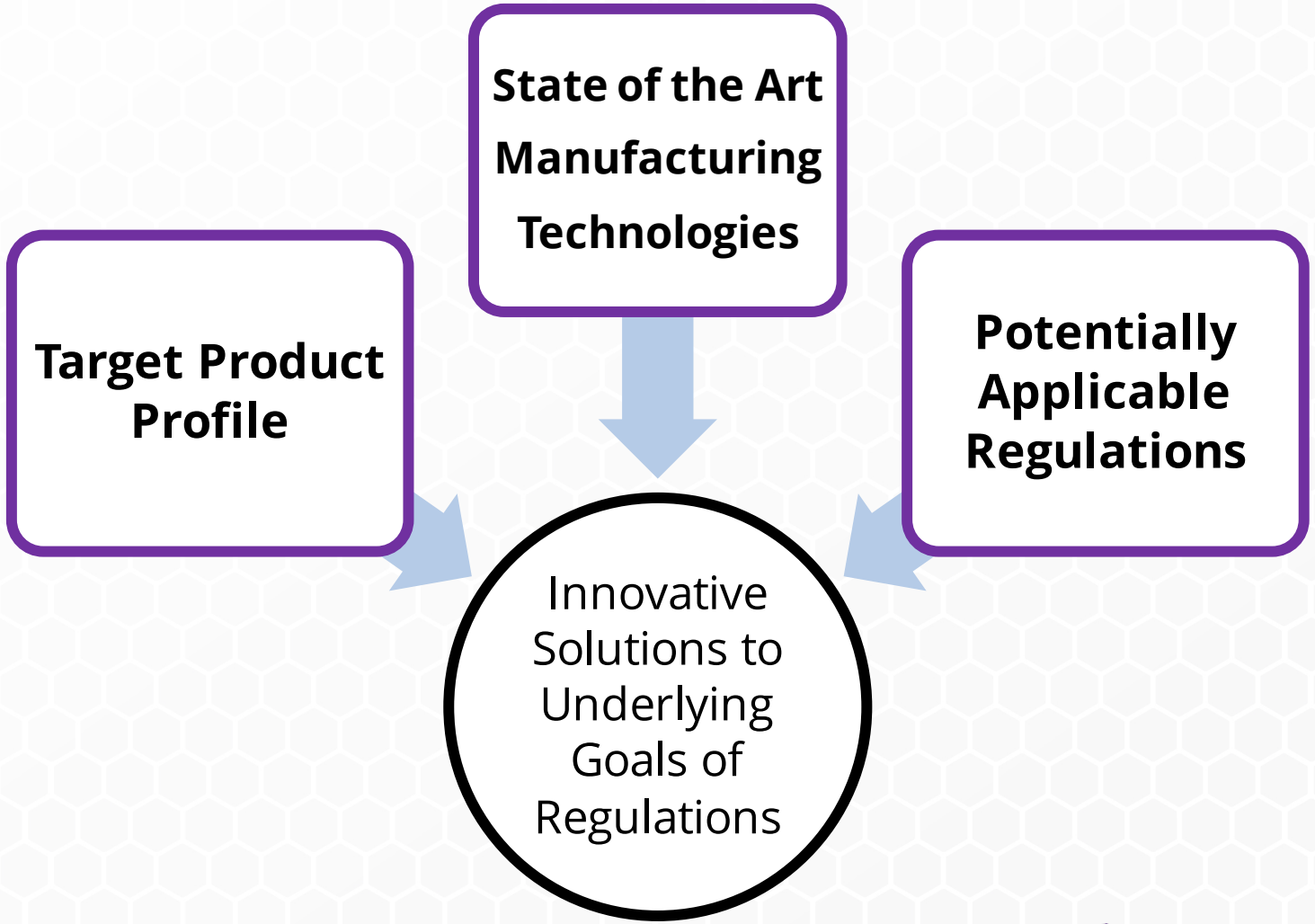
- A subset of DM that uses manufacturing units distributed to host sites in proximity to patient care (e.g., health care facilities) where:
  - Drugs are intended to be administered to patients.
  - Manufacturing units are neither intended for personal, in-home use nor drug compounding (i.e., drugs will adhere to the specification of an approved regulatory submission).
  - The host sites are not applicants or typical manufacturers and *do not source active pharmaceutical ingredients (APIs)* or excipients for use in a manufacturing unit.
  - The end user is not a traditional manufacturing operator; their quality responsibilities are minimized and in accordance with established instructions by the applicant (e.g., assembling the components of the POC unit and activating validated software).

Source: "Distributed Manufacturing and Point-of-Care Manufacturing of Drugs", FDA/CDER, 10/22

Motivations to Attempt DMor POCfor CGTManufacturing

- Increased Availability of Advanced Therapies for Patients
- More Streamlined Logistics
  - Source Material (API)
  - Final Product
- Scale Out of Manufacturing for Small Lot Sizes
  - Orphan Indications
  - Personalized Indications
  - Autologous Therapies
- Risk and Revenue Sharing for Provider/Producer

Approach for Applying Regulations to Innovative Products or Processes



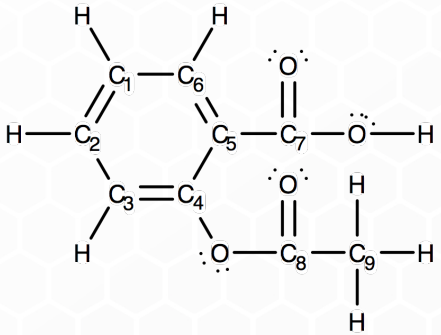
Current cGMP Regulations

- Provide for systems that assure proper design, monitoring, control of manufacturing processes/facilities
- Compliance with cGMP regulations assures drug/biologic products meet their quality standards and helps prevent instances of contamination, mix-ups, deviations, failures, and errors.

Must keep these underlying regulatory goals in mind

Challenge: Design of Quality Systems and Oversight for CGT Products under DM/POC Manufacturing Models

- Regulations (600's, 820's, 1271's, 210/211's) all designed in ensure safety and effectiveness of simpler products manufactured under conventional centralized manufacturing processes
- However CGT Products are orders of magnitude more complex



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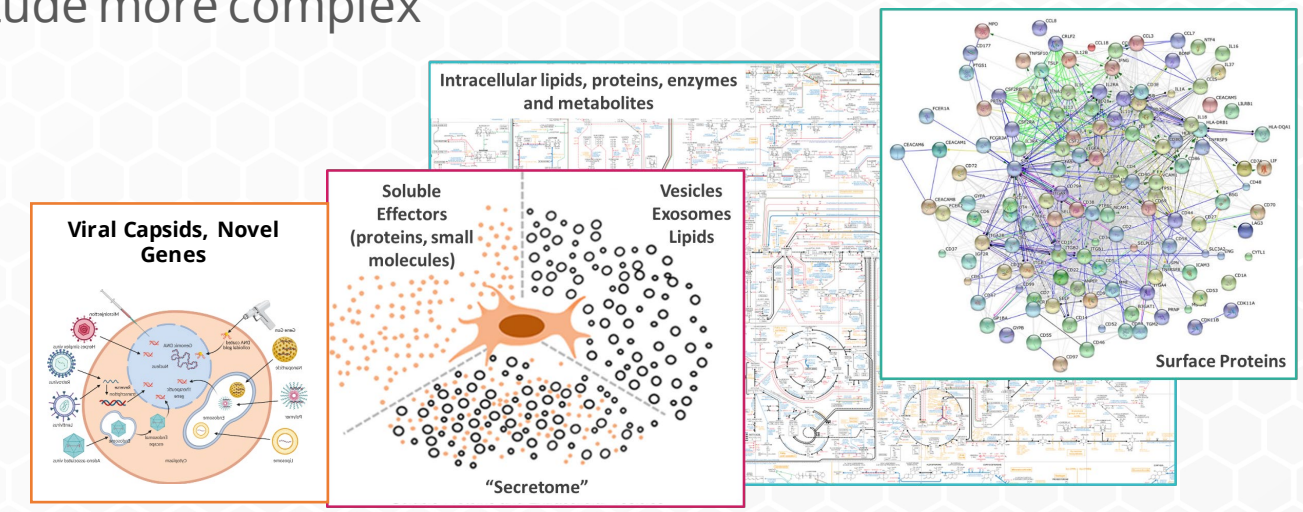


CGT Products Are Complex Relative to Traditional Drugs and Biotech

Challenge: Design of Quality Systems and Oversight for CGT Products under DM/ POC Manufacturing Models

- Regulations (600's, 820's, 1271's, 210/211's) all designed in ensure safety and effectiveness of simpler products manufactured under conventional centralized manufacturing schemes.
- Current CGT product manufacturing predominantly resembles traditional, manual research methods
- Specialized automation for specific classes of CGT are beginning to be introduced

Research and Development

Manufacturing

Most Current CGT Manufacturing Processes Are Neither Scalable Nor Easily Distribute

Potential Challenges to DMF or POC for CGT Manufacturing

Lack of Clarity WRT Degree of Regulatory Flexibility to Expect

- Establishment for Biologics (600.3(w))-> Facility in Sec. 351 of PHSA
- For HCT/P, Establishment (1271.3(b))
- Sterility Testing (610.12)
- Potency Testing (610.10)

DMF/POC Regulatory Solution Needs to Allow a Degree of Variation Along a General P

Not Purely "Case by Case"

Potentia Challenges to Mor POC for CGT Manufacturing

- Inadequate Sensors for At-line & In-Line Analysis of Unit Operations and Lot Release
  - Inadequate Number of Analytes Identified During Product Development
    - Confusion between hypotheses and scientific laws
    - Confusion between research and product development
  - Inadequate Verification and Validation of Analyses

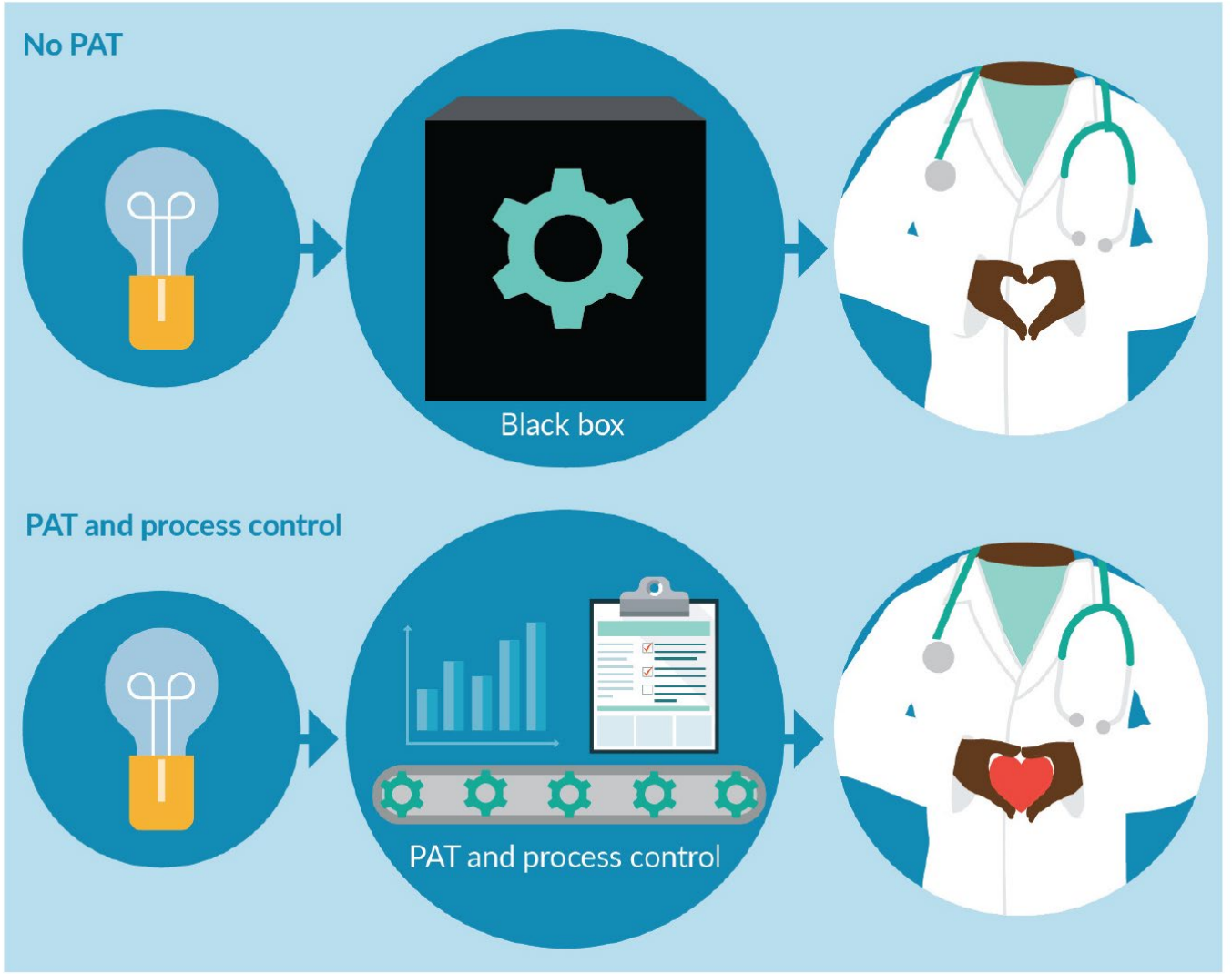
What might a prototype to test manufacture of products from throughout the Regenerative Medicine Spectrum lo

For a review of sensors for biofabrication,see McCorry *et al* 2022 *Biofabrication* in press https://doi.org/10.1088/1758-5090/ac94a1

Generalized Gene, Cell, Tissue and Organ Manufacturing F

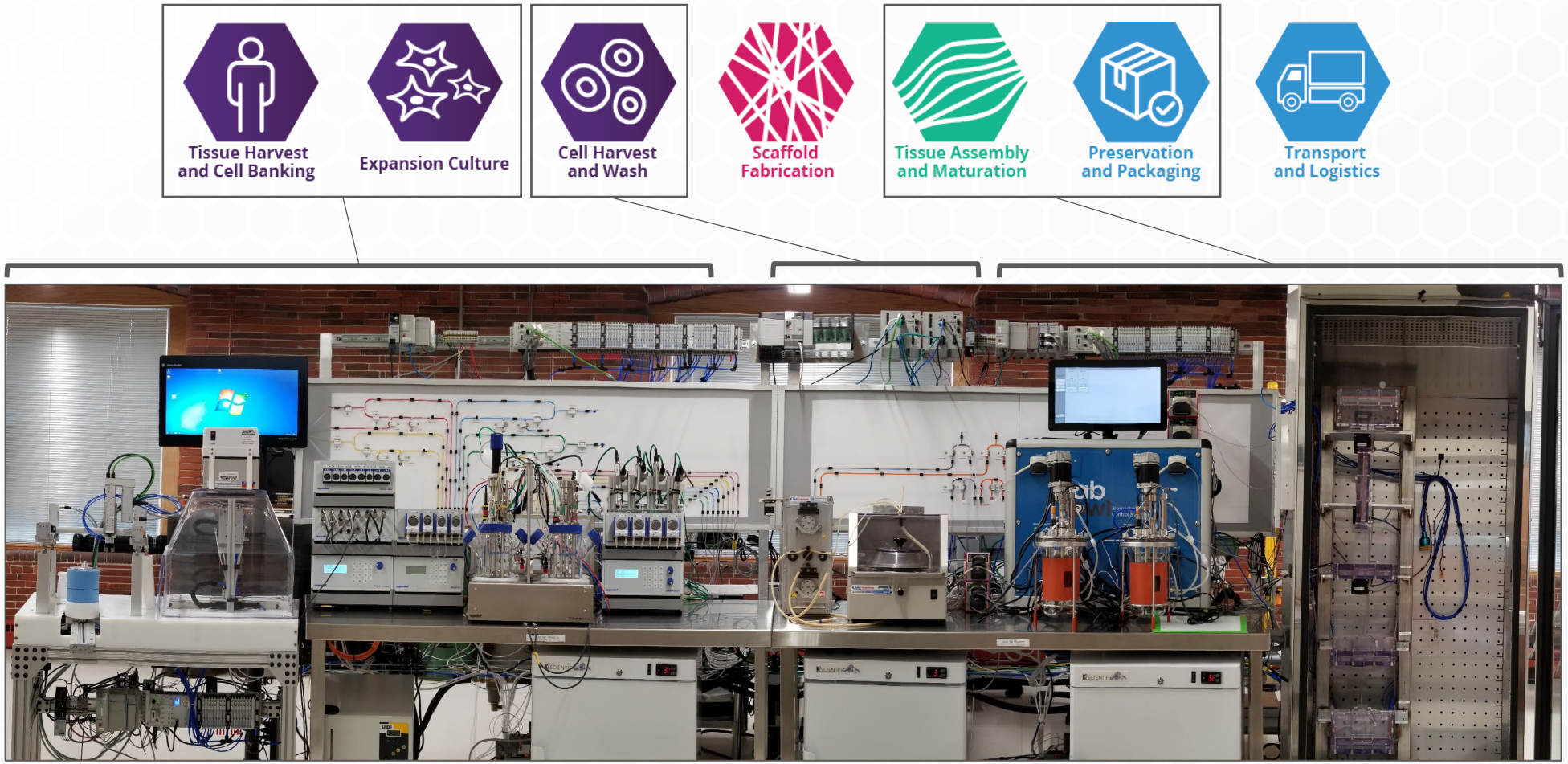
Applicable to both Cells and GT Vectors

Concept: Scalable, Modular, Automated and Closed manufacturing



Source McCorry et al., *Cell & Gene Therapy Insights* 2020; 6(10), 1477–1488

Tissue Foundry: a prototype SMAC manufacturing system



Next Generation Manufacturing Practices Will Be More Amenable to Distributed and/or Point of Care Manufacturing

- Adapt processes to scalable manufacturing equipment
- Integrate equipment through automation to decrease variability and facilitate distributed manufacturing
- Close processes to mitigate contamination risk, facilitate manufacturing in a variety of environments and drive down costs
- Increased use of PAT and QbD principles
  - Develop objective in-process and final product quality control specifications
- Centralize quality assurance
  - Distributed manufacturing sites must transparently and reliably transmit data to the Central PQS Unit
  - Enable parametric release of product
  - Eliminate post release batch testing

THANK YOU