U.S. FOOD & DRUG ADMINISTRATION

CBER's Perspective on Distributed Manufacturing and Point-of-Care Manufacturing of Complex Biologics

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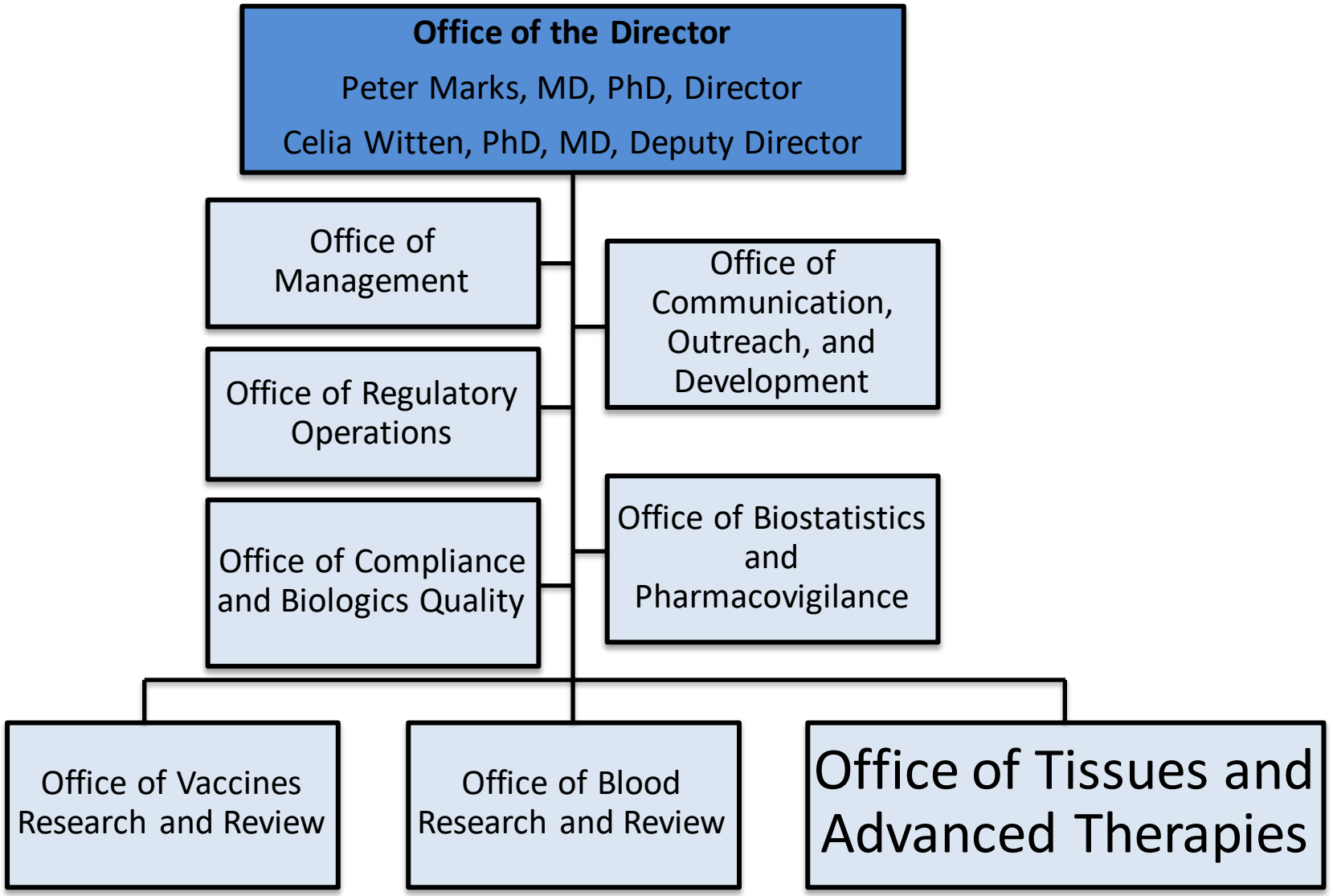
FDA/PQRI Workshop on the Regulatory Framework for Distributed and Point of Care Pharmaceutical Manufacturing: An Opportunity for DM/POC Stakeholder Engagement
November 16, 2022

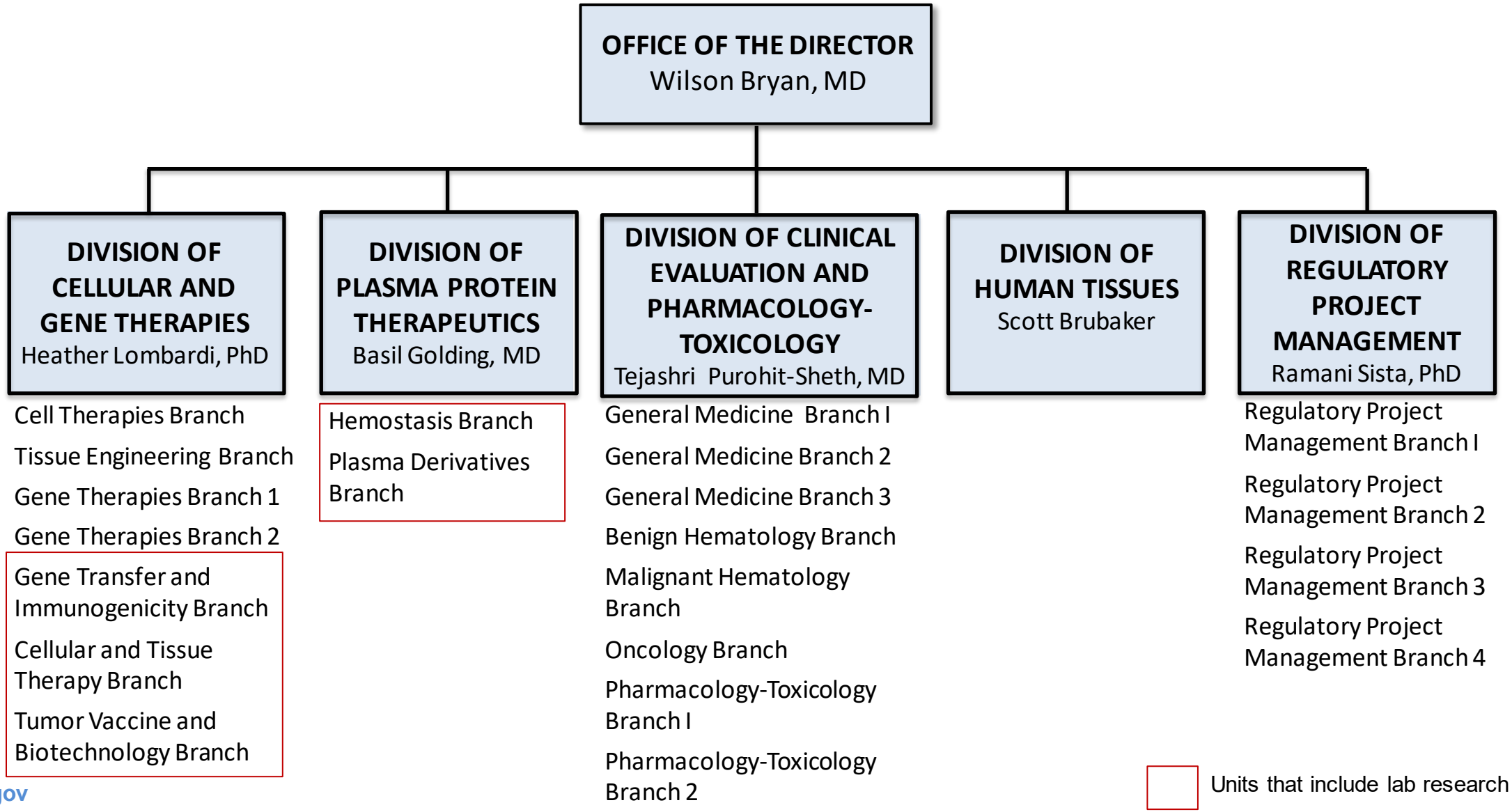
Overview

- CBER/OTAT Overview
- Regulatory Framework for Cell & Gene Therapy Products
- Manufacturing Strategies for Cell & Gene Therapy Products
- Summary

Center for Biologics Evaluation and Research (CBER)



Office of Tissues and Advanced Therapies (OTAT)



Units that include lab research

Examples of OTAT-Regulated Products

- Stem cells/stem cell-derived
  - Adult (e.g., hematopoietic, neural, cardiac, adipose, mesenchymal)
  - Perinatal (e.g. placental, umbilical cord blood)
  - Fetal (e.g. neural)
  - Embryonic
  - Induced pluripotent stem cells (iPSCs)
- Functionally mature/differentiated cells (e.g., retinal pigment epithelial cells, pancreatic islet cells, chondrocytes, keratinocytes)
- Products for xenotransplantation
- Tissues
- Devices
- Combination products
  - Tissue-engineered and regenerative medicine products
- Therapeutic vaccines and cellular immunotherapies including antigen-specific and active immunotherapies
- Gene therapies
  - Genetically-modified cells
  - Replication-competent vectors
  - Non-viral vectors
  - Viral vectors
  - Genome editing products
  - Genetically modified organisms
- Blood products
  - Coagulation factors
  - Fibrin sealants
  - Fibrinogen
  - Thrombin
  - Plasminogen
  - Immune globulin
  - Venom antisera for snakes, scorpions, and spiders

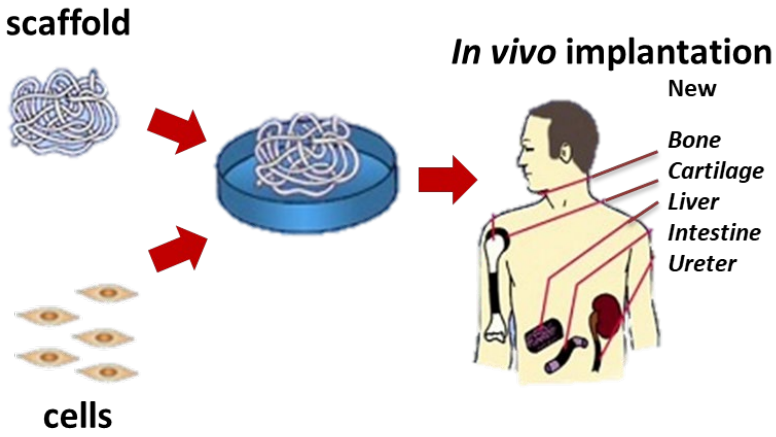
REGULATORY FRAMEWORK FOR CELL & GENE THERAPY PRODUCTS

Regulatory Framework for Cell & Gene Therapy Products

- Human Cells, Tissues & Cellular and Tissue-Based Products (HCT/Ps)
  - 21 CFR 1271
- Biological Products
  - 21 CFR 600s
- Drugs
  - 21 CFR Part 312 Investigational New Drug (IND)
  - 21 CFR Parts 210/211 Current Good Manufacturing Practices

Regulatory Framework for Cell & Gene Therapy-Device Combination Products

- Device (e.g., when a structural scaffold is used in combination with cells or when a delivery device is used)
  - 21 CFR 800s
    - 21 CFR 820 Quality System Regulations
- Combination Products
  - 21 CFR Parts 3 and 4



Human Cells, Tissues, and Cellular and Tissue-based Products (HCT/Ps)

- **Definition:** Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer to a human recipient (21 CFR 1271.3 d).
- **Examples of HCT/Ps**
  - Musculoskeletal tissue, skin, ocular tissue, human heart valves; vascular graft, dura mater, reproductive tissue/cells,
  - Stem/progenitor cells; other cellular therapy products
  - Cells transduced with gene therapy vectors
  - Combination products (e.g., cells or tissue + device)
- **Not HCT/Ps**
  - Blood and blood products; xenografts – separate regulatory pathways
  - Minimally manipulated unrelated donor bone marrow – overseen by Health Resources and Services Administration (HRSA)
  - Vascularized human organs – overseen by HRSA
  - Secreted or extracted products (e.g., human milk, collagen, cell factors)

21 CFR 1271

21 CFR 1271	Issues Addressed
Subpart A: General Provisions	Definitions, criteria for regulatory pathways determination (361 tissue vs. drug, device, and/or biologic)
Subpart B: Establishment Registration and Listing	Applicability: types and uses of products that will be regulated by these rules, requirements for registering and listing establishments/products
Subpart C: Donor Eligibility Determination	Requirements for donor screening and testing for "relevant communicable disease agents and diseases"
Subpart D: Current Good Tissue Practice (CGTP)	Handling and Process controls to prevent contamination and introduction, transmission or spread of communicable diseases; requirements for manufacturing
Subpart E: Additional requirements	Adverse reaction and deviation reporting; labeling
Subpart F: Inspection and enforcement	Inspection, importation, orders of retention, recall, destruction and cessation of manufacturing

B, E & F apply to 361 HCT/Ps only, the rest apply to both 361 & 351 HCT/Ps.

21 CFR 600s

- 21 CFR 610: General Biological Products Standards
  - Safety
    - Sterility (bacterial and fungal sterility): 21 CFR 610.12
    - Communicable Disease Agents: 21 CFR 610.40 / 21 CFR 1271 Subpart C: Donor Eligibility
  - Purity (21 CFR 610.13)
    - Free of extraneous materials in the manufacturing process
    - Test for pyrogenic substances (endotoxin)
  - Identity (21 CFR 610.14)
    - Specific test to distinguish it from others

21 CFR 600s

- Constituent materials (21 CFR 610.15)
  - Ingredients, Preservatives, Diluents, Adjuvants, Excipients
- Potency (21 CFR 610.10)
  - Assay for relevant biological activity
- Product release requirements
  - Tests prior to release required for each lot (21 CFR 610.1)
  - Testing and release for distribution (21 CFR 211.165)

21 CFR 210/211

- 21 CFR 210: Current Good Manufacturing Practice in Manufacturing Processing, Packing, or Holding of Drugs
- 21 CFR 211: Current Good Manufacturing Practice for Finished Pharmaceutical
  - Subpart A: General Provisions
  - Subpart B: Organization and Personnel
  - Subpart C: Buildings and Facilities
  - Subpart D: Equipment
  - Subpart E: Control of Components and Drug Product Containers and Closures
  - Subpart F: Production and Process Controls
  - Subpart G: Packaging and Labeling Control
  - Subpart H: Holding and Distribution
  - Subpart I: Laboratory Controls
  - Subpart J: Records and Reports
  - Subpart K: Returned and Salvaged Drug Products

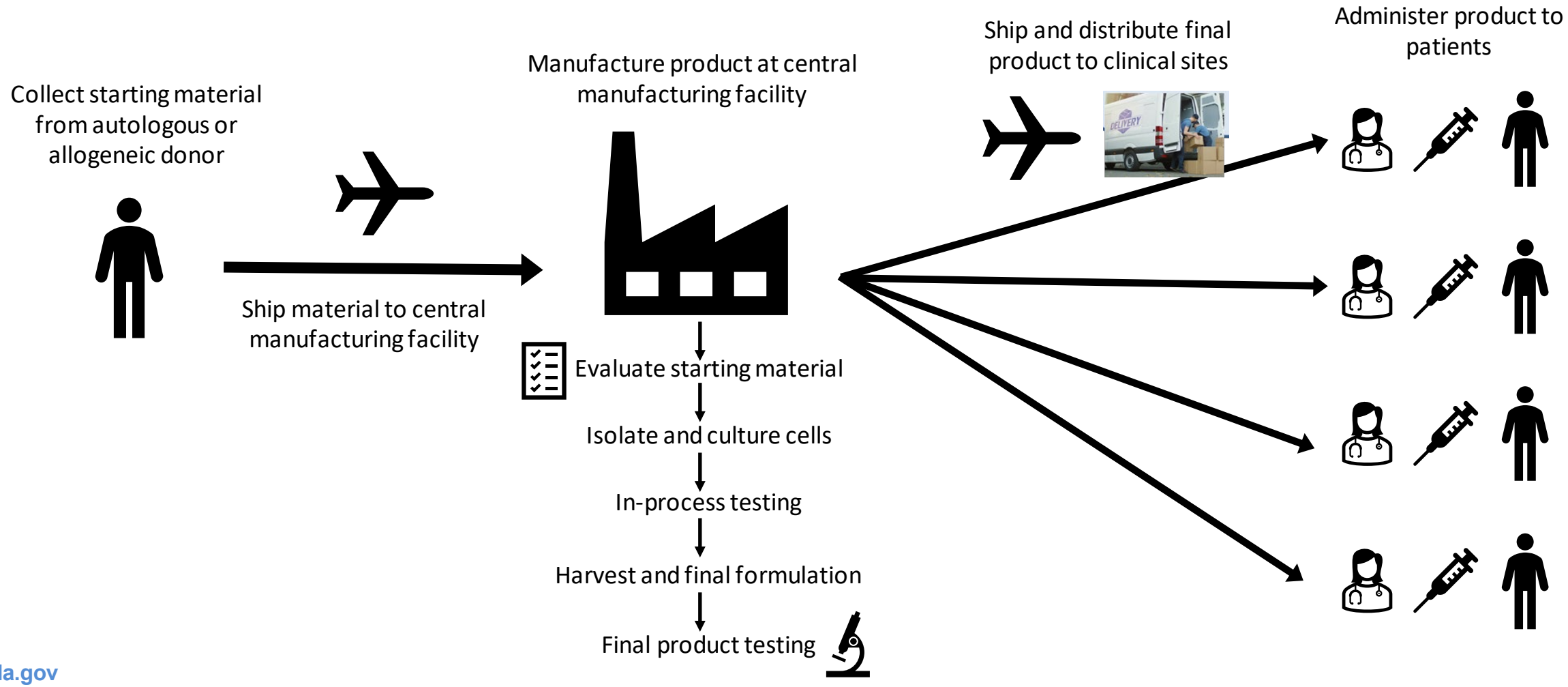
21 CFR 210/211

- Current Good Manufacturing (cGMP) regulations are enforced by FDA
  - 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.

MANUFACTURING STRATEGIES FOR CELL & GENE THERAPY PRODUCTS

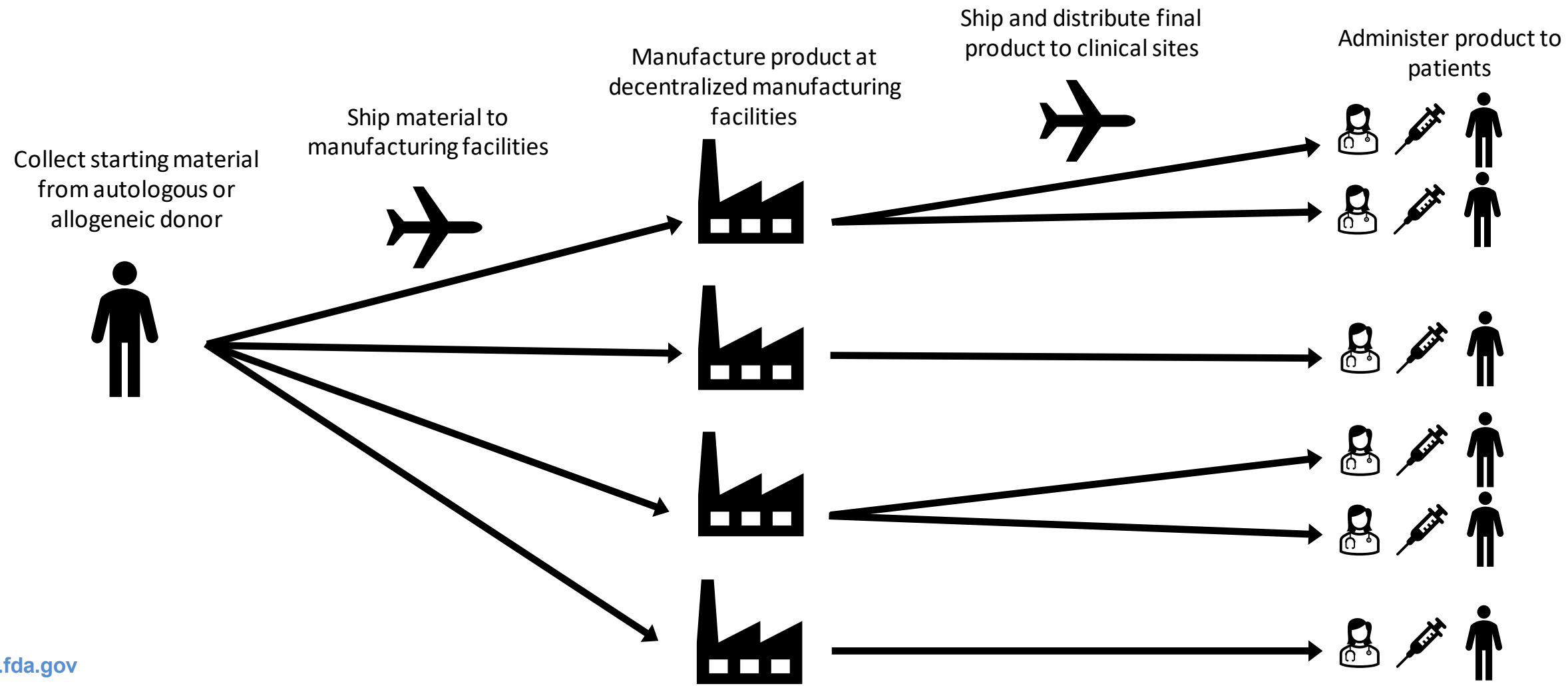
Centralized Manufacturing

- Centralized manufacturing strategy typically consists of a manufacturing facility producing the product and distributing to end users



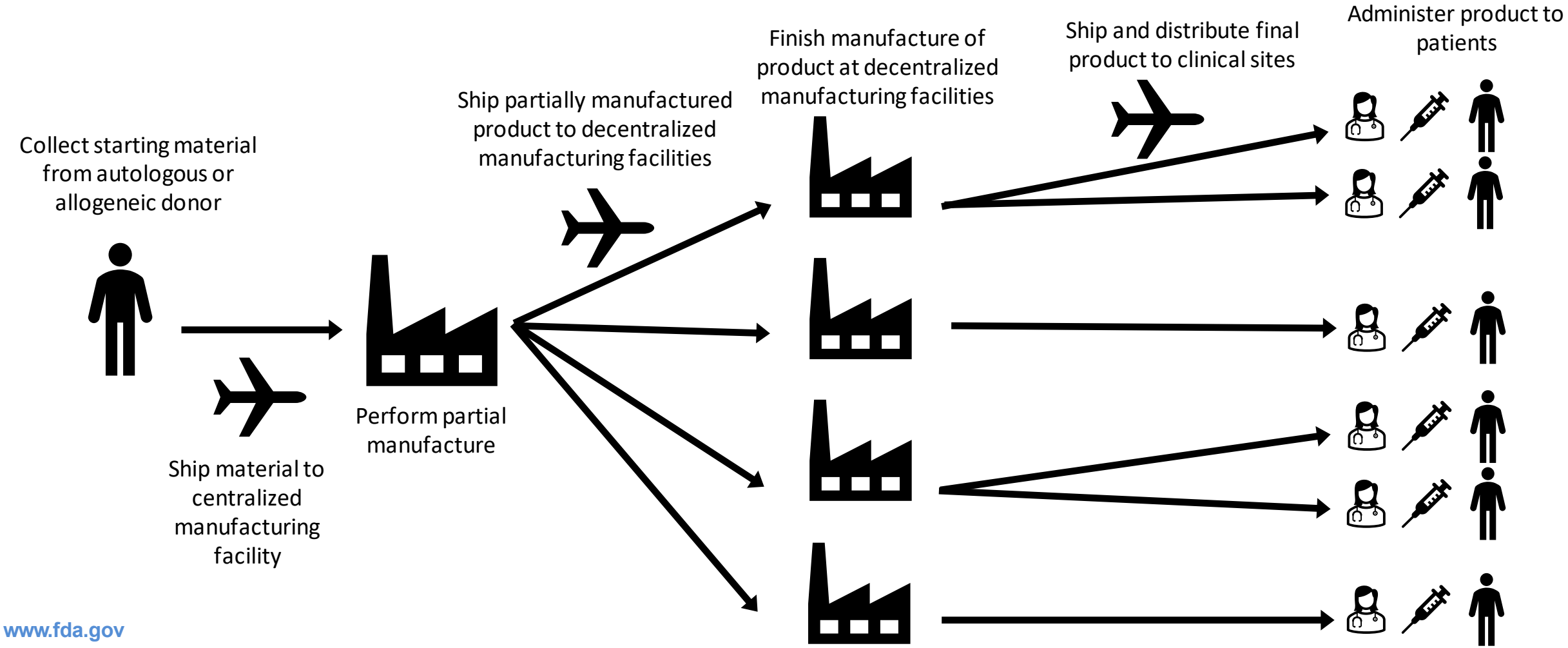
Distributed Manufacturing (DM)

- Manufacturing occurs at multiple locations (decentralized facilities)
  - Manufacturing is replicated and geographically dispersed to shorten supply chains and increase supply reliability



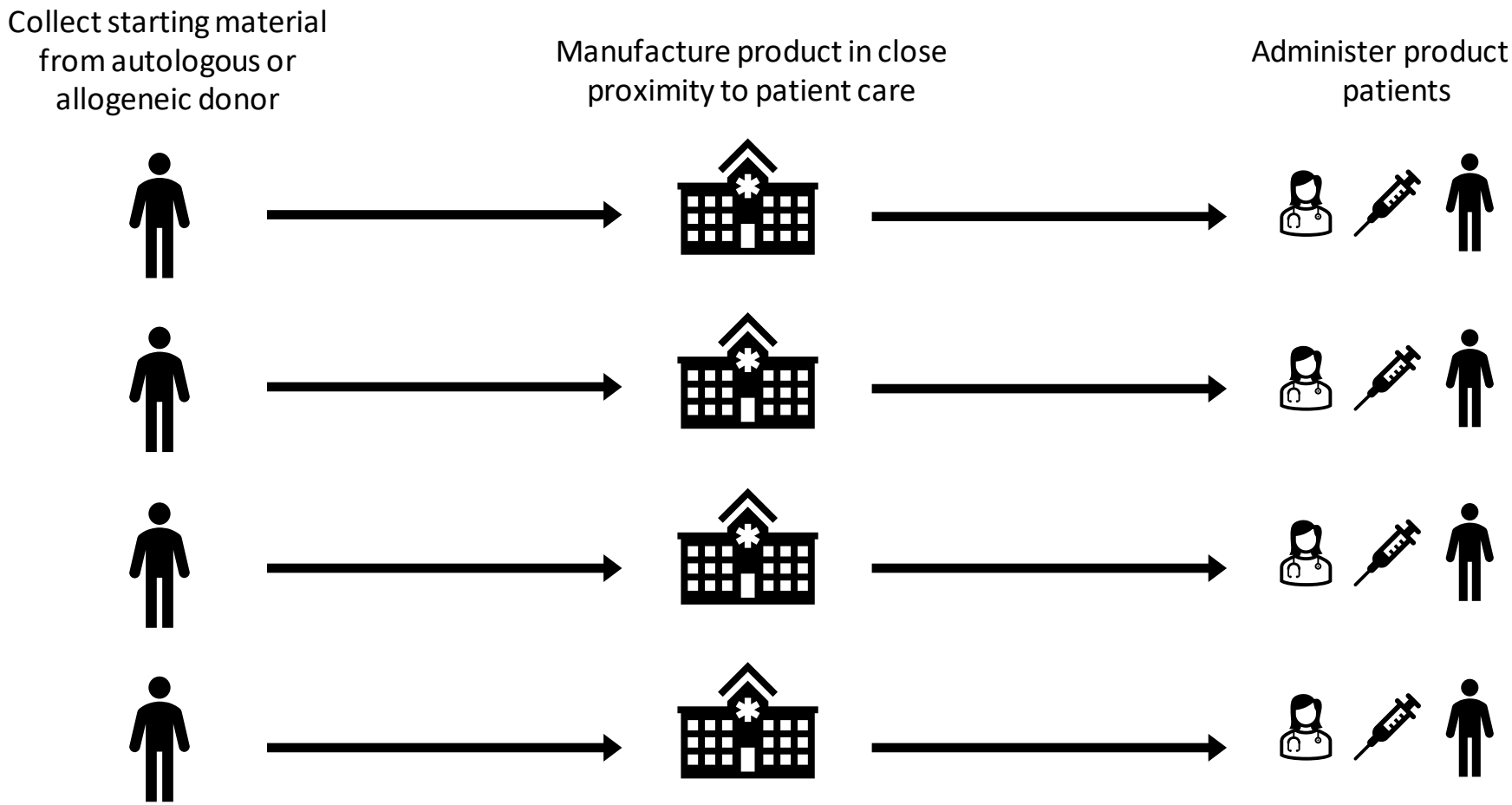
Distributed Manufacturing (DM)

- Manufacturing occurs at multiple locations (decentralized facilities)
  - Manufacturing is replicated and geographically dispersed to shorten supply chains and increase supply reliability
  - Manufacturing may initially take place at a centralized facility



Point-of-Care (POC) Manufacturing

- Manufacturing occurs at host sites in close proximity to patient care



Regulatory Expectations – IND/BLA Pathway

- All scenarios require full compliance with regulatory requirements in accordance with IND and BLA regulations

- Cell or gene therapy product would need to be manufactured according to cGMPs at all sites
- Each manufacturing site would need to be registered and inspected prior to licensure

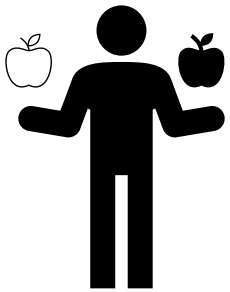
- Each site would be considered a Contract Manufacturing Organization (CMO) and, if performing product testing, a Contract Testing Organization (CTO)

Regulatory Expectations – IND/BLA Pathway

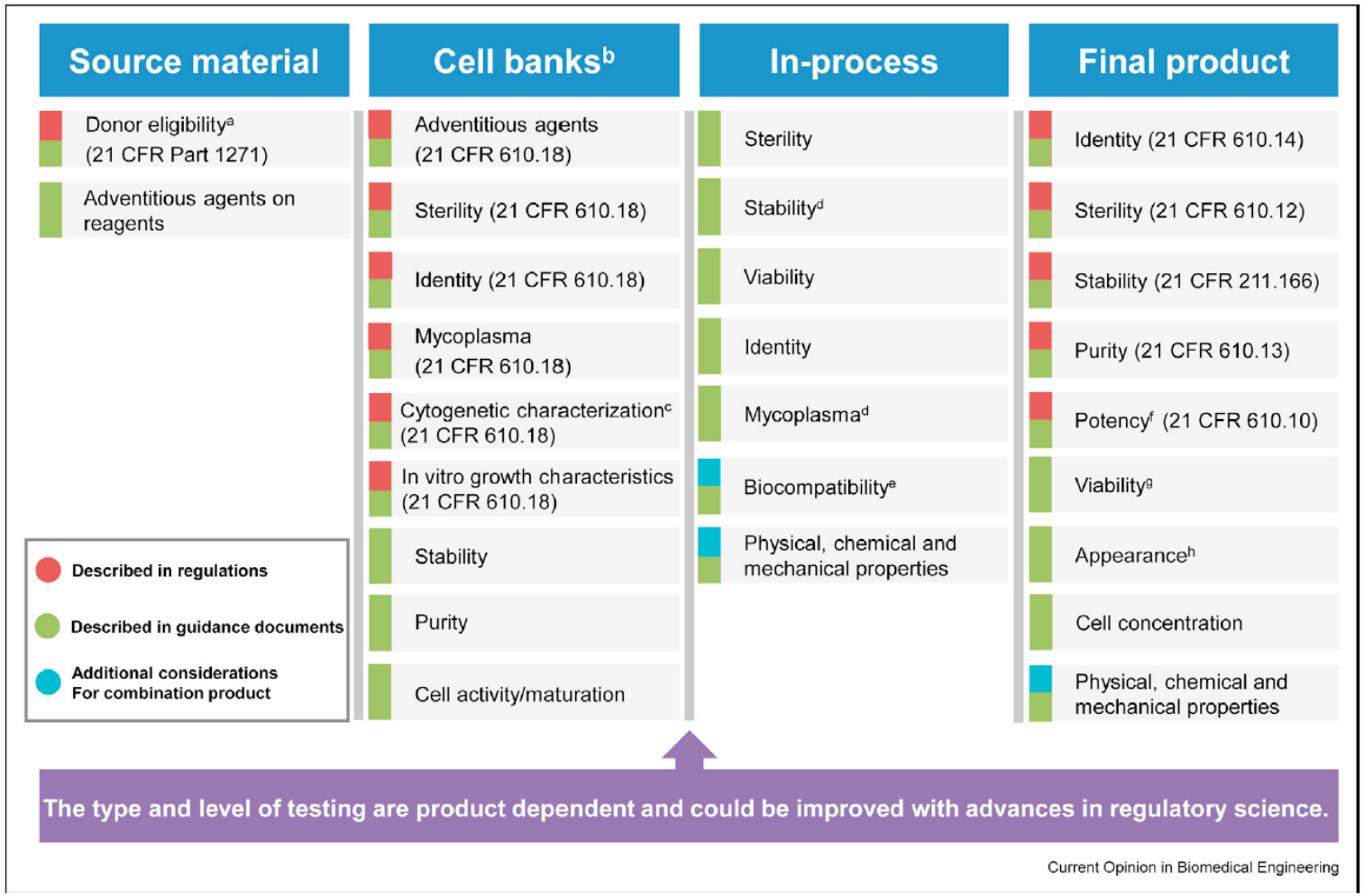
- IND sponsor would need to qualify the manufacturing process and confirm that all regulations are being followed at each manufacturing facility

- IND sponsor would need to ensure the same manufacturing process is being followed at all facilities, including in-process and final product testing and procedures

- IND sponsor also needs to demonstrate and establish that a comparable product is being manufactured at each CMO, and that comparable analytical assays are performed at each CTO



Typical In-Process and Final Product Testing for Cell & Gene Therapy Products



J. Lam, K.E. Sung, S.S. Oh. *Science-based regulatory considerations for regenerative medicine cellular products.* Curr. Opin. Biomed. Eng., 21 (2022), Article 100361.

Point-of-Care Devices

- There may be situations where a cell or gene therapy product manufactured at POC may be regulated under a POC device paradigm
- When regulated as a device, FDA would regulate the therapy, comprising:
  - A device used to process a biological starting material, and
  - The cellular output, which is administered to the patient for a therapeutic purpose

Point-of-Care Devices

- Regulatory device pathways may include:
  - 510(k) for Class II devices to demonstrate substantial equivalence to a predicate
  - IDE and PMA for Class III devices to demonstrate safety and effectiveness
- Devices intended to process HCT/Ps ex vivo to create a therapeutic article have been assigned to CBER. Examples include:
  - Cell sorters used at POC to isolate and/or concentrate autologous stem cells for in vivo use
  - Devices that process autologous blood or tissue to produce a new HCT/P at POC for direct re-administration

Point-of-Care Devices

- To be regulated under the device authorities:
  - The instrument/device (and output) should be used at the point of care (i.e., processing is performed at and by the clinical site where the output is administered); such an instrument/device is referred to as a 'POC device'
  - A POC device (including its output) should be intended to be used for a specific clinical indication
  - The instrument should generally be responsible for preparing the output in a ***reproducible and controlled manner***

Point-of-Care Devices

- To be regulated under the device authorities:
  - The instrument should be able to ensure that the output is of ***sufficient quality*** for the specific clinical indication
    - Considerations of 'sufficient quality' are product specific
    - Under POC device paradigm, the quality of the device output is controlled through the performance characteristics of the device and adequate labeling and instructions for use
      - Generally, sponsors are requested to test/characterize the device output during clinical studies to support that the device is capable of consistently producing an output that is of sufficient quality and safety

Manufacturing Equipment vs POC Device

- Equipment used in the manufacture, processing, packing, or holding of a drug product shall be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for its cleaning and maintenance (21 CFR 211.63)
  - Subject to installation qualification (IQ), operation qualification (OQ), and performance qualification (PQ) and cGMP requirements at each 'site/facility'
  - IQ is a verification of alignment with design specifications
  - OQ is a verification of alignment with functional specifications
  - PQ is a verification of the ability of a process to meet with user required specifications

Manufacturing Equipment vs POC Device

- Instrument used to manufacture cell or gene therapy product under IND/BLA would be considered manufacturing equipment and not regulated as a device
  - E.g., Instrument used for in vitro enrichment or depletion of cells from human heterogeneous hematologic cell populations which will undergo further processing in CAR-T and other T-cell therapies would be considered manufacturing equipment and reviewed under a biologics license application (BLA) for a cell or gene therapy product and not as a standalone device. However, if instrument is intended to produce a therapeutic article suitable for direct administration without further processing, then different requirements may apply.

Current Regulatory Approach

- Current CBER/OTAT approach considers products on a ***risk-based*** and ***case-by-case basis***
  - Sponsors are encouraged to engage with Agency via INTERACTs, Pre-submissions (Type B pre-IND, Q-submissions), Type C Facility meeting, or CBER Advanced Technologies Team (CATT) meeting to discuss information, regulatory pathway, and regulatory requirements

Summary

- Cell and gene therapy products can be manufactured under centralized, distributed, or point-of-care manufacturing
- Applicable IND/BLA regulations must be followed, regardless of where the cell or gene therapy product is manufactured
- Cell and gene therapy products manufactured at POC may be regulated under a POC device paradigm under certain limited situations
- Engage with FDA regarding any questions related to regulatory pathway and requirements

Useful FDA Information

- References for the Regulatory Process for the Office of Tissues and Advanced Therapies (OTAT): http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/OtherRecommendationsforManufacturers/ucm094338.htm
- Cellular & Gene Therapy Guidances: https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances
- Interactions with Office of Tissues and Advanced Therapies: https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/interactions-office-tissues-and-advanced-therapies
- CATT Program: https://www.fda.gov/vaccines-blood-biologics/industry-biologics/cber-advanced-technologies-team-catt

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- **OTAT Learn Webinar Series:**

  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm

- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm
- **Office of Combination Products (OCP):** http://www.fda.gov/CombinationProducts/default.htm
- **Phone:** 1-800-835-4709 or 240-402-8010
- **Consumer Affairs Branch**: ocod@fda.hhs.gov
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