CBER Perspective on Decentralized Manufacturing

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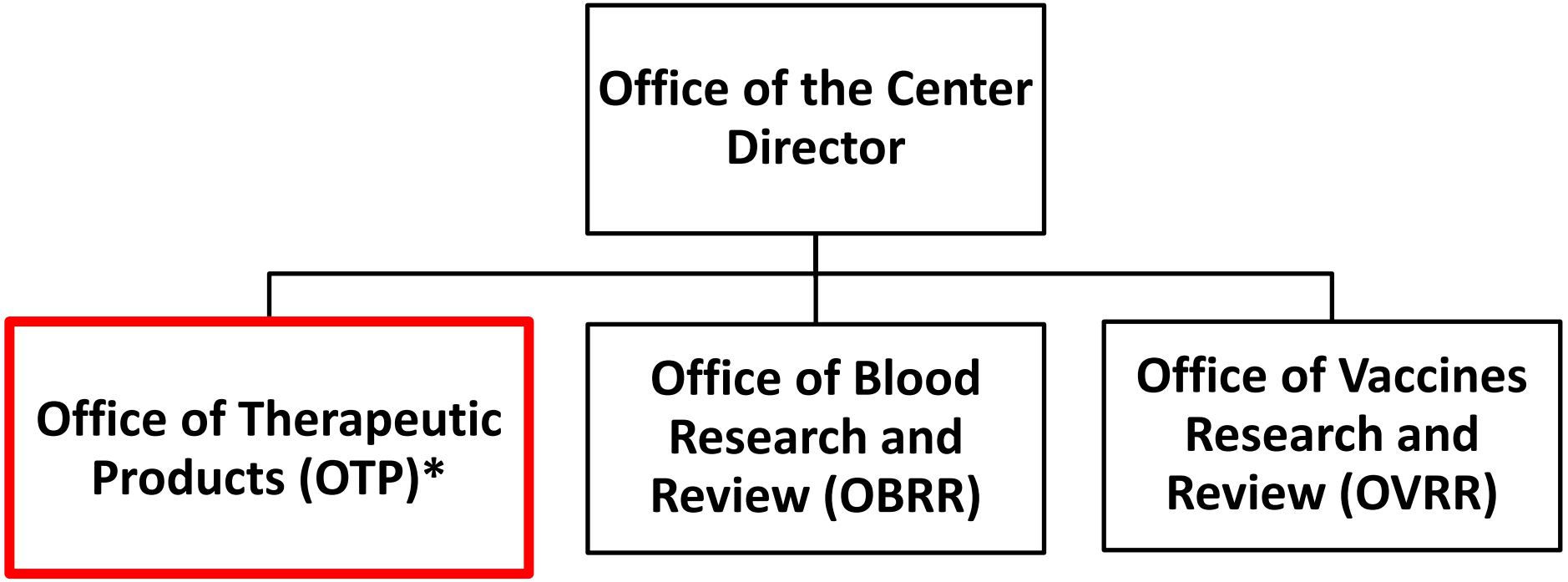
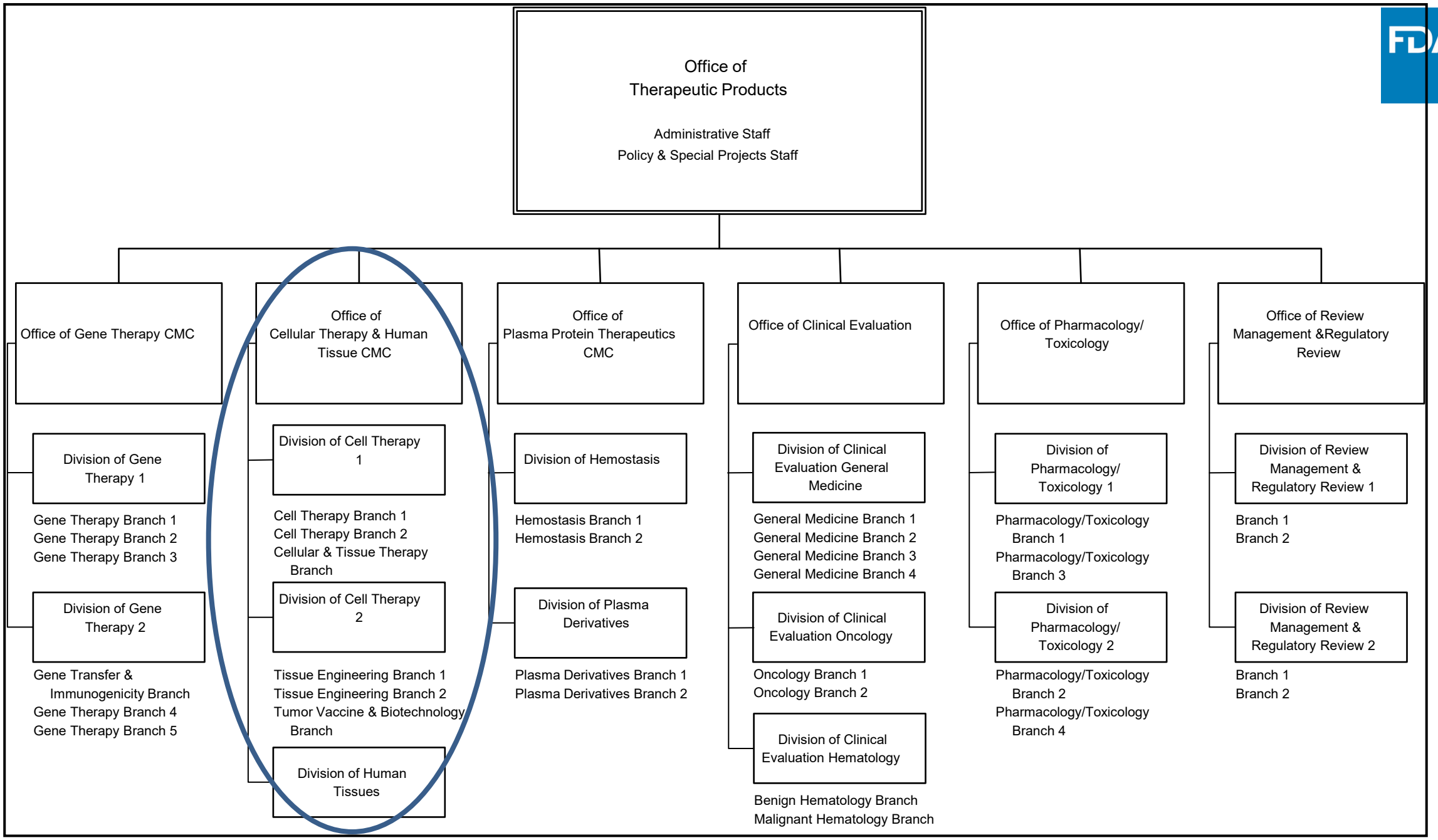
NASEM Emerging Technologies and Innovation in Manufacturing Regenerative Medicine Therapies: A Workshop
October 17, 2023

Center for Biologics Evaluation and Research (CBER) - Product Review Offices



*Formerly the Office Tissue and Advanced Therapies (OTAT)


Office of
Therapeutic Products
Administrative Staff
Policy & Special Projects Staff
Office of Gene Therapy CMC
Division of Gene Therapy 1
Gene Therapy Branch 1
Gene Therapy Branch 2
Gene Therapy Branch 3
Division of Gene Therapy 2
Gene Transfer & Immunogenicity Branch
Gene Therapy Branch 4
Gene Therapy Branch 5
Office of Cellular Therapy & Human Tissue CMC
Division of Cell Therapy 1
Cell Therapy Branch 1
Cell Therapy Branch 2
Cellular & Tissue Therapy Branch
Division of Cell Therapy 2
Tissue Engineering Branch 1
Tissue Engineering Branch 2
Tumor Vaccine & Biotechnology Branch
Division of Human Tissues
Office of Plasma Protein Therapeutics CMC
Division of Hemostasis
Hemostasis Branch 1
Hemostasis Branch 2
Division of Plasma Derivatives
Plasma Derivatives Branch 1
Plasma Derivatives Branch 2
Office of Clinical Evaluation
Division of Clinical Evaluation General Medicine
General Medicine Branch 1
General Medicine Branch 2
General Medicine Branch 3
General Medicine Branch 4
Division of Clinical Evaluation Oncology
Oncology Branch 1
Oncology Branch 2
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Benign Hematology Branch
Malignant Hematology Branch
Office of Pharmacology/ Toxicology
Division of Pharmacology/ Toxicology 1
Pharmacology/Toxicology Branch 1
Pharmacology/Toxicology Branch 3
Division of Pharmacology/ Toxicology 2
Pharmacology/Toxicology Branch 2
Pharmacology/Toxicology Branch 4
Office of Review Management &Regulatory Review
Division of Review Management & Regulatory Review 1
Branch 1
Branch 2
Division of Review Management & Regulatory Review 2
Branch 1
Branch 2

Diversity of OTP - Regulated Products

- **Gene therapies (GT)**
  - Ex vivo genetically modified cells
  - Non-viral vectors (e.g., plasmids)
  - Replication-deficient viral vectors (e.g., adenovirus, adeno-associated virus, lentivirus)
  - Replication-competent viral vectors (e.g., measles, adenovirus, vaccinia)
  - Human genome editing products
  - Microbial vectors (e.g., Listeria, Salmonella)
- **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)
- **Products for xenotransplantation**

- **Functionally mature/differentiated cells** (e.g., retinal pigment epithelial cells, pancreatic islets, chondrocytes, keratinocytes)
- **Therapeutic vaccines and other antigen-specific active immunotherapies**
- **Blood- and Plasma-derived products**
  - Coagulation factors
  - Fibrin sealants
  - Fibrinogen
  - Thrombin
  - Plasminogen
  - Immune globulins
  - Anti-toxins
  - Venom antisera for scorpions, snakes, and spiders
- **Combination products**
  - Engineered tissues/organs
- **Devices**
- **Tissues**

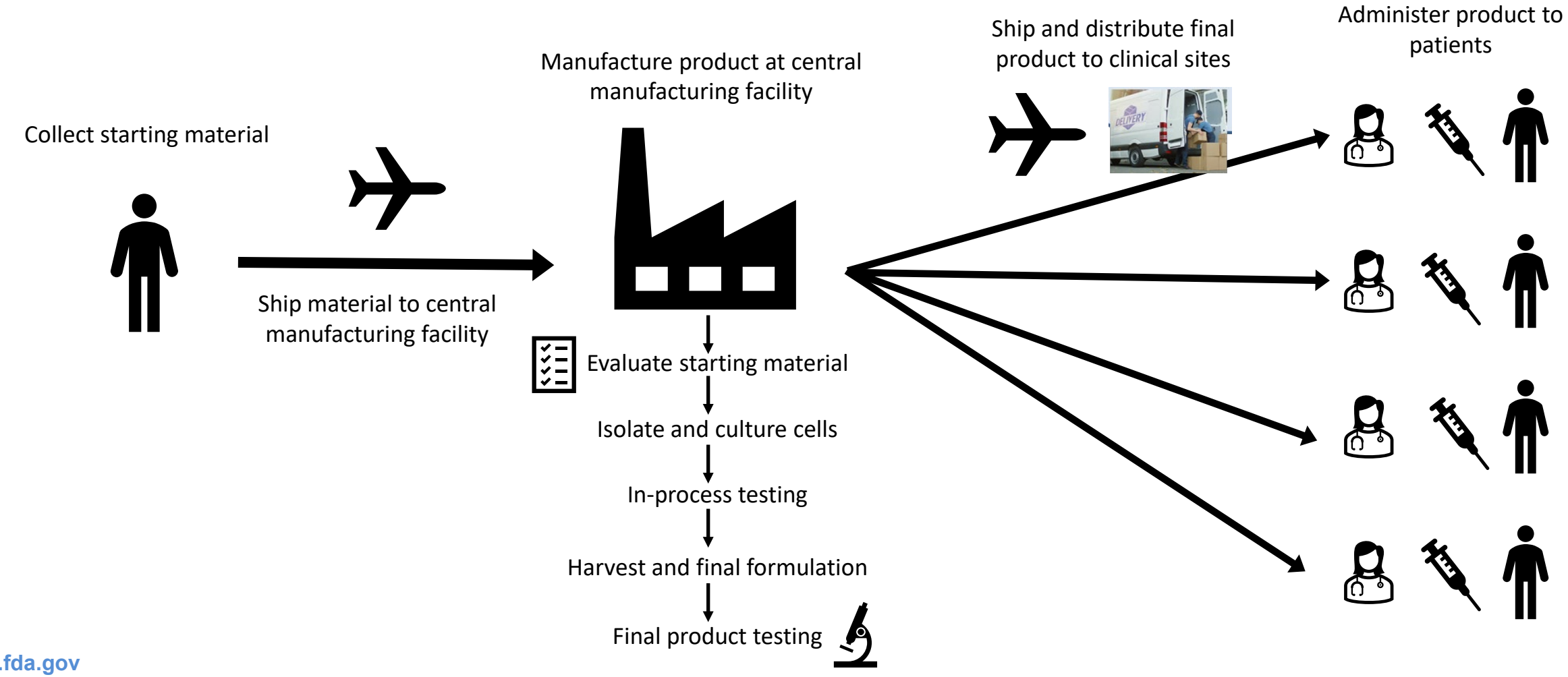
MANUFACTURING STRATEGIES FOR CELL & GENE THERAPY PRODUCTS

Preface

- Regulatory considerations only represent our current thinking
- ***No regulatory guidance or policy established yet*** for ***cell and gene therapies*** manufactured using ***point of care (POC)*** and/or ***distributed manufacturing models***
- Several paradigms and their applicability to CBER products are being actively considered currently
  - Not yet finalized
  - Providing general advice/feedback at this point is still challenging
- Current CBER/OTP approach considers products on a ***case-by-case basis*** per the level of development for each product
  - 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

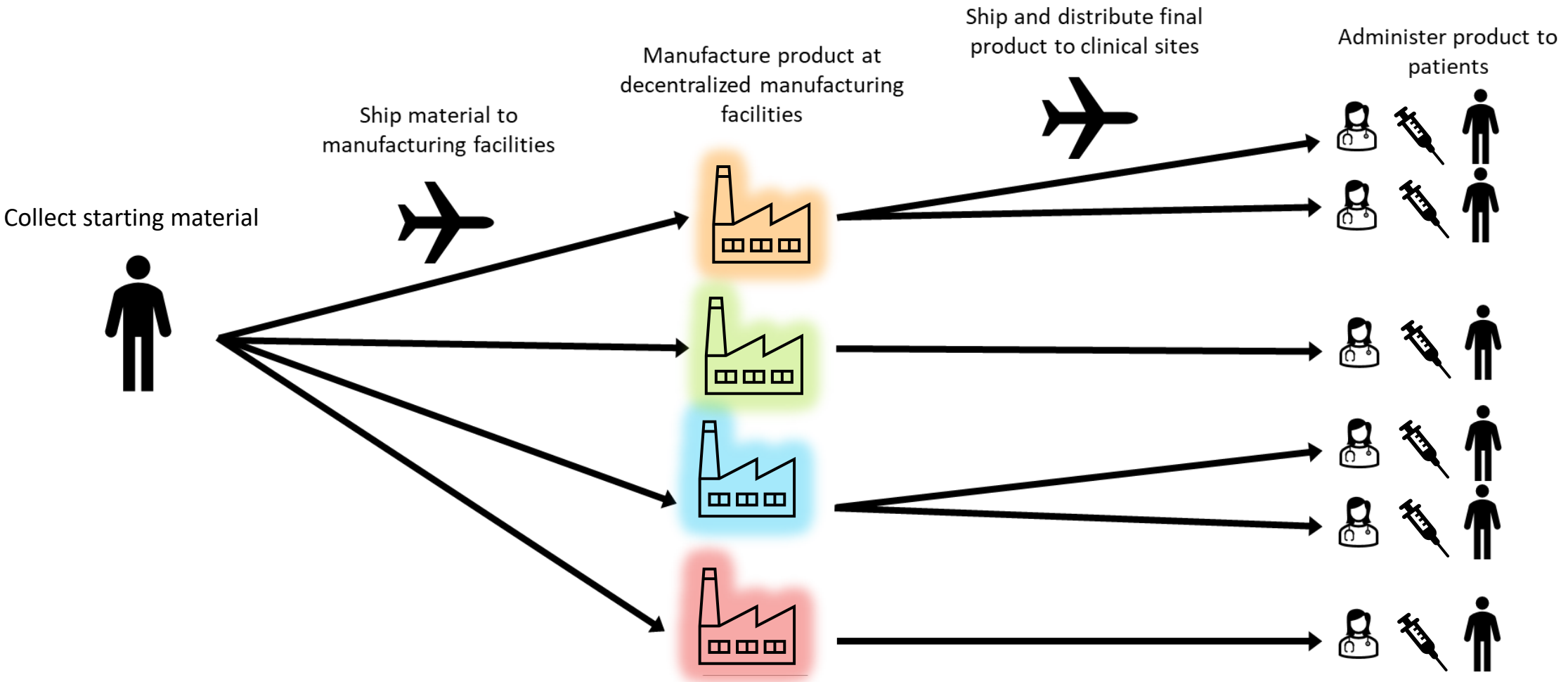
Centralized Manufacturing

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



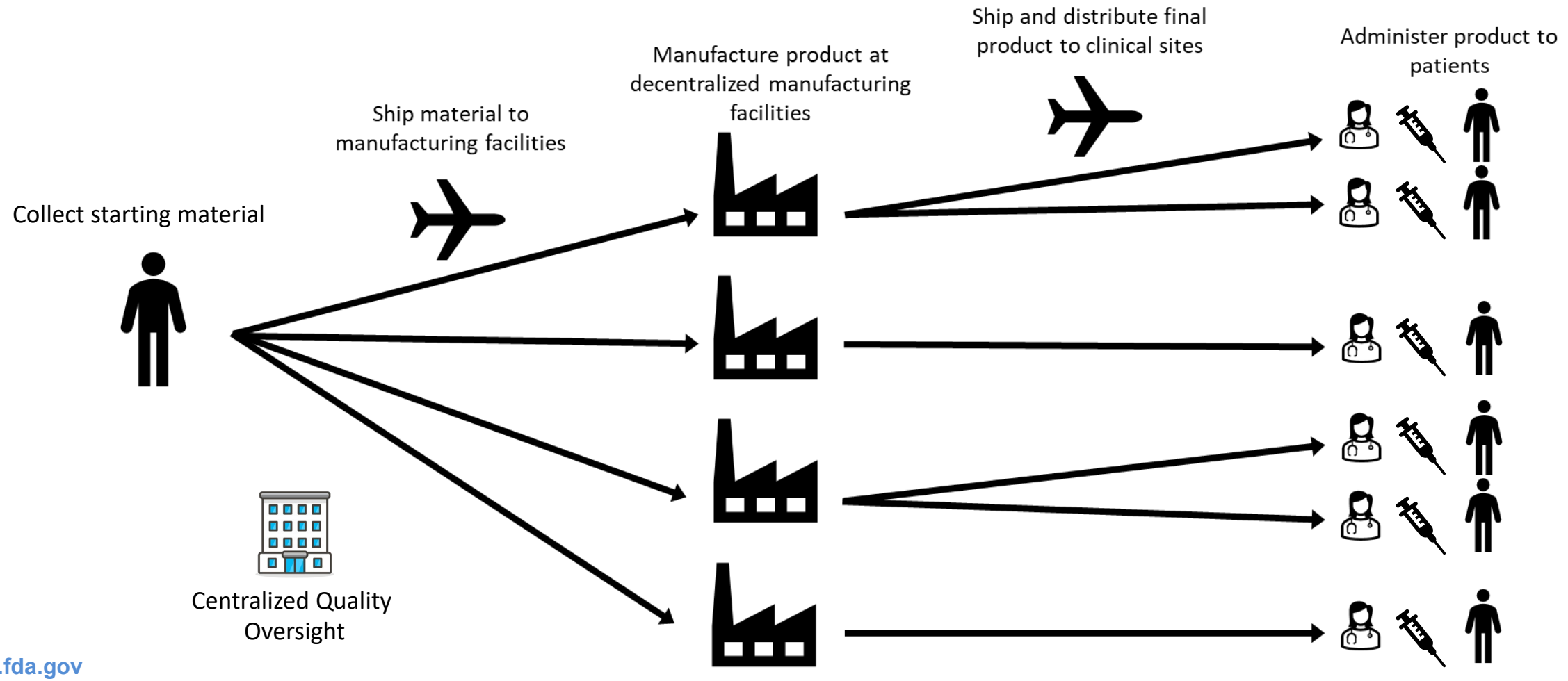
Decentralized Manufacturing (DM)

- Manufacturing occurs at multiple locations (decentralized facilities)



Distributed Manufacturing (DM)

- Manufacturing occurs at multiple locations (decentralized facilities)
  - Manufacturing is replicated and geographically dispersed to shorten supply chains and increase supply reliability
  - Oversight of the manufacturing operations under a single unified quality system located at a central site



Distributed Manufacturing (DM)

- Manufacturing occurs at multiple locations (decentralized facilities)
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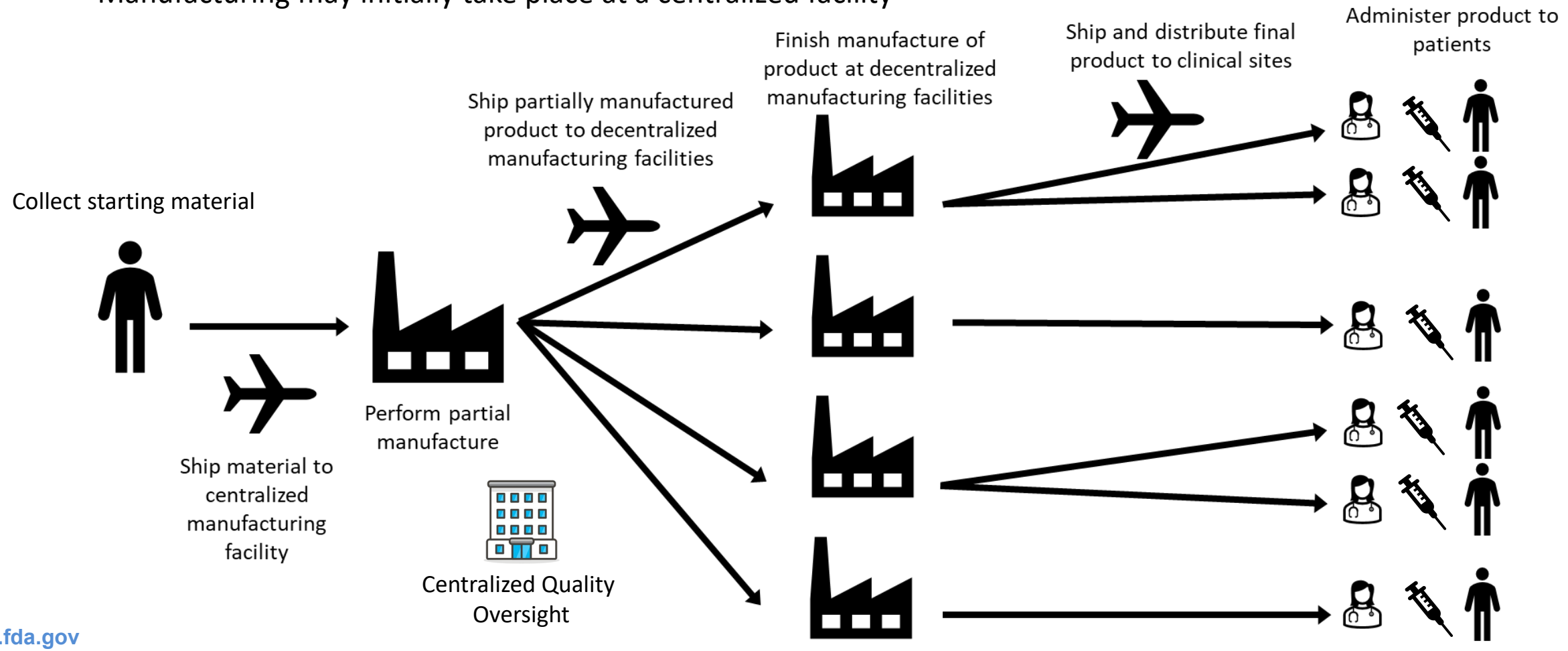
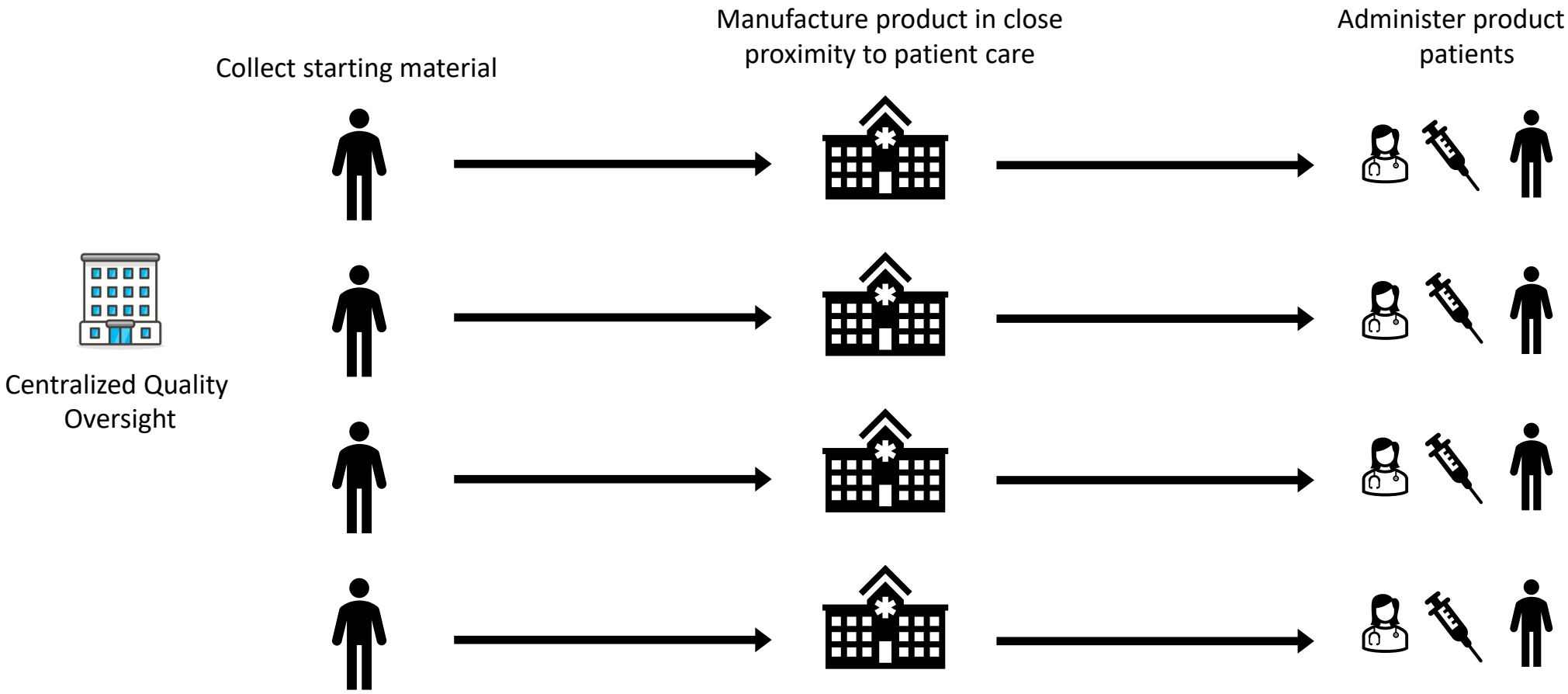
  - Oversight of the manufacturing operations under a single unified quality system located at a central site
  - Manufacturing may initially take place at a centralized facility



Point-of-Care (POC) Manufacturing

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

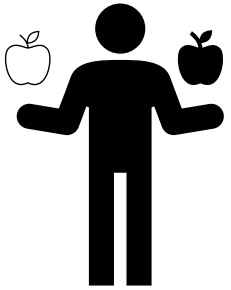


POC Manufacturing Example

- 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
- CAR T and other T cell therapies are ***biological products*** subject to regulation under the Public Health Service Act (42 U.S.C. 262), and the Federal Food, Drug and Cosmetic Act (FD&C) Act ***as drugs (21 U.S.C. 321(g))***.
  - FDA approval under a ***Biologics License Application*** (BLA) to legally market biologic for a specified indication requires demonstration that the product is safe, pure, and potent
  - Clinical trials of biologic would be conducted under an ***Investigational New Drug*** (IND) in compliance with 21 CFR 312
  - Instrument used would be considered manufacturing equipment and reviewed under an IND and BLA for the biologic

Regulatory Expectations – IND/BLA Pathway

- All scenarios require full compliance with regulatory requirements in accordance with IND and BLA regulations
- At each site, the IND sponsor must:
  - ensure the same manufacturing process is being followed at all facilities, including in-process and final product testing and procedures
  - qualify the manufacturing process and confirm that all regulations and CGMPs are being followed at each manufacturing facility
  - demonstrate that the product and analytical assays are comparable at each site
- Each manufacturing site would need to be registered and inspected prior to licensure



FDA INITIAVES TO SUPPORT ADVANCED MANUFACTURING

Framework for Regulatory Advanced Manufacturing Evaluation (FRAME)

Stakeholder engagement to support advanced manufacturing

1. Seek and analyze input to ensure FDA's understanding of advanced manufacturing technologies is thorough and its analysis of the regulatory framework is science- and risk-based.
2. Address risks to ensure regulations and policy are compatible with future advanced manufacturing technologies.
3. Clarify expectations for stakeholders implementing advanced manufacturing.
4. Harmonize to ensure global regulatory practice is clear to stakeholders implementing advanced manufacturing.

Seek and Analyze Input

Facilitated Stakeholder Input:

- **Distributed and Point-of-Care Manufacturing Discussion Paper in Federal Register** Published 10/14/22
- **FDA/PQRI Distributed and Point-of-Care Manufacturing Public Workshop** (November 14-16, 2022)

Highlights from FDA/PQRI Distributed and Point-of-Care Manufacturing Public Workshop CBER Session 6: Panel Discussion

- Discussion of challenges associated with DM/POC Manufacturing of Cell and Gene Therapy products, which include:
  - Aseptic processing, manual manipulations, analytical comparability challenges, small batch sizes and short shelf life, complex biological starting materials, novel reagents, analytical testing
  - Assay comparability across multiple sites
  - Site-to-site variability and detection of drift in product quality
- POC settings may present additional challenges related to:
  - Unqualified cleanrooms not suitable for open manipulation steps, deficient PQS, supply chain and GMP deficiencies, personnel, and lack of quality control laboratories and/or equipment
  - Timing and availability of lot release

Highlights from FDA/PQRI Distributed and Point-of-Care Manufacturing Public Workshop CBER Session 6: Breakout Discussions with Stakeholders

- Challenges related to site-to-site consistency and conformity of processes across multiple sites
- Challenges with keeping track of chain of custody
- The role of end users at host sites for POC manufacturing –how should healthcare workers be trained/certified; frequencies of runs may vary across POC host sites and could impact experience level
- Advanced (in-line) analytics may not be suitable/mature for measuring quality attributes of CGTs (e.g., potency)
- Stakeholders would like guidance on comparability and streamlining regulatory submissions
- Degree of manual manipulation vs. automated processing at POC may vary depending on product (e.g., tissue engineered products)

Stakeholder Feedback: Expected Outcomes

- Clarified regulatory expectations to facilitate the implementation of DM and POC technologies for human drug and biologic products.
- Assurance that regulations and policies are compatible with DM and POC strategies for human drug and biologic products.
- International harmonization on the regulation of DM technologies to facilitate adoption for human drug and biologic products.

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- **OTP (OTAT) Learn Webinar Series:**

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