

U.S. FDA's Perspective on Delivery Devices Used to Administer Cell and Gene Therapy Products

Laura Ricles, PhD

Branch Chief
Tissue Engineering Branch 1
Division of Cell Therapy 2
Office of Cellular Therapy and Human Tissue
Office of Therapeutic Products, CBER/FDA

CASSS Cell & Gene Therapy Products (CGTP): Manufacturing, Quality and Regulatory Considerations
June 27, 2023

Overview

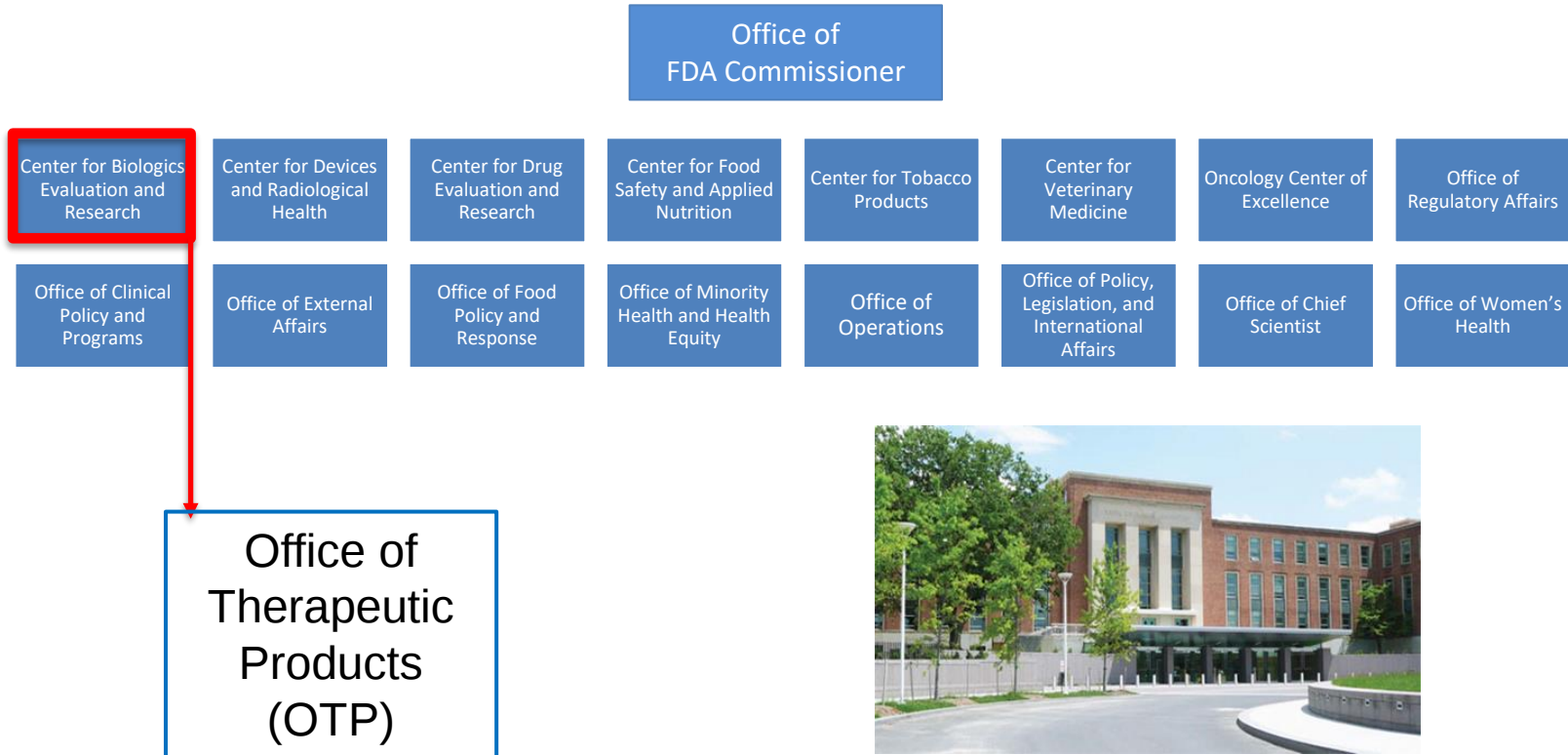


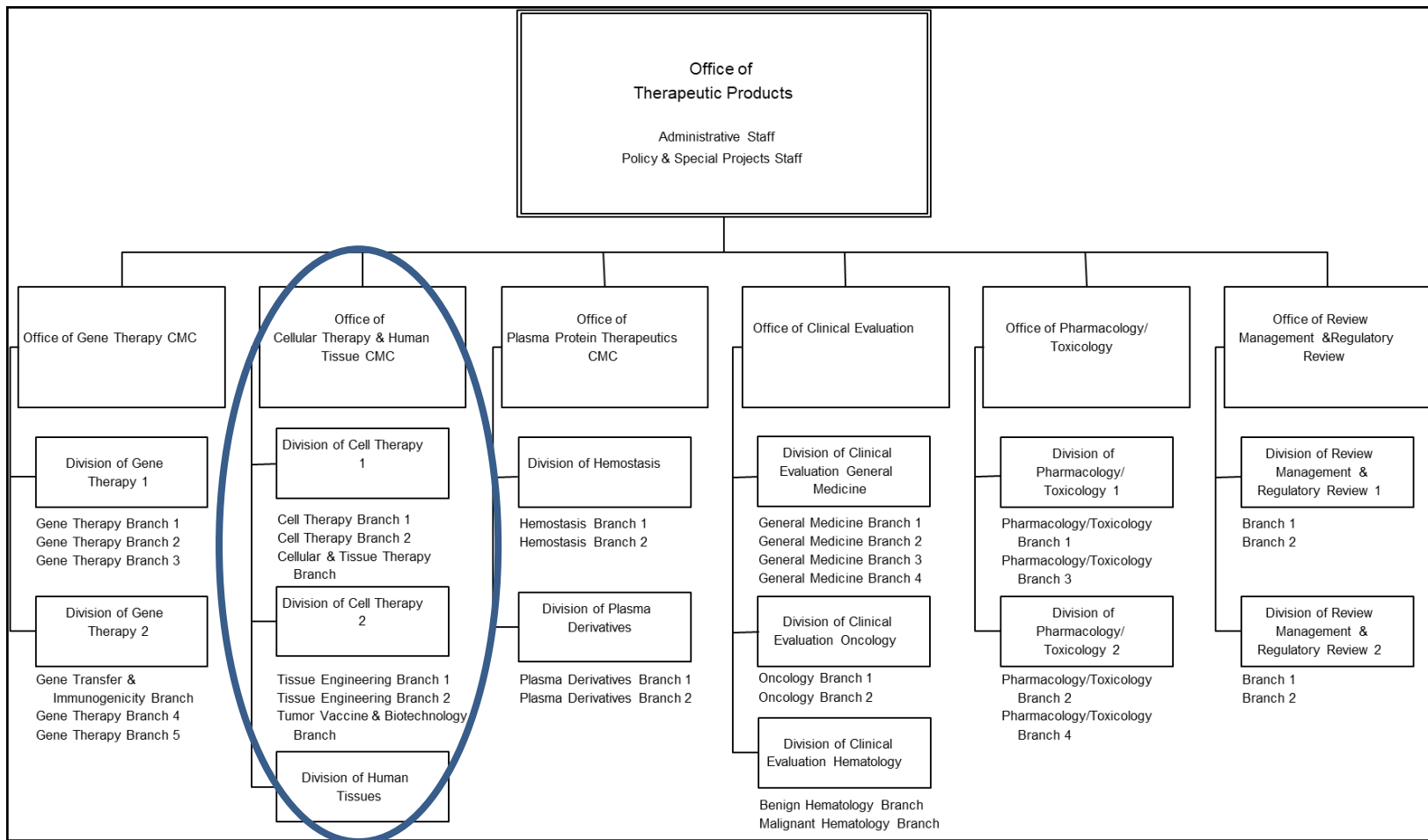
- FDA Organization
- Delivery Device Considerations and Regulatory Requirements
- Regulatory Submissions and Interacting with OTP
- Summary



FDA ORGANIZATION

FDA Organization





Diversity of Products Regulated by Office of Therapeutic Products (OTP) in CBER



- **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, vaccinia)
 - Microbial vectors (e.g., Listeria, Salmonella)
 - Genome-edited 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)
 - 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 immunotherapies**
- **Blood- and Plasma-derived products**
 - Coagulation factors, fibrinogen, thrombin
 - Fibrin sealants
 - Plasminogen
 - Immune globulins
 - Anti-toxins
 - Snake venom antisera
- **Combination products**
 - Engineered tissues/organs
- **Devices**
- **Tissue-based products**



DELIVERY DEVICE CONSIDERATIONS AND REGULATORY REQUIREMENTS

What is a Device?

Definition of “Device” 201(h)

The term “device” means an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is –

- (1) recognized in the official National Formulary, or the U.S. Pharmacopoeia, or any supplement to them,
- (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or
- (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action ... which is not dependent upon being metabolized for the achievement of its primary intended purposes.

What is a Delivery Device?

Cell Therapy

Gene Therapy

Delivery
Device*



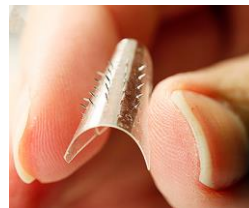
Syringe and
Needle



Jet Injector



Microneedle Patch



Intrabronchial Spray Device



***Not including** scaffolds, wound coverings, or encapsulation materials which are typically considered to provide more than a delivery function

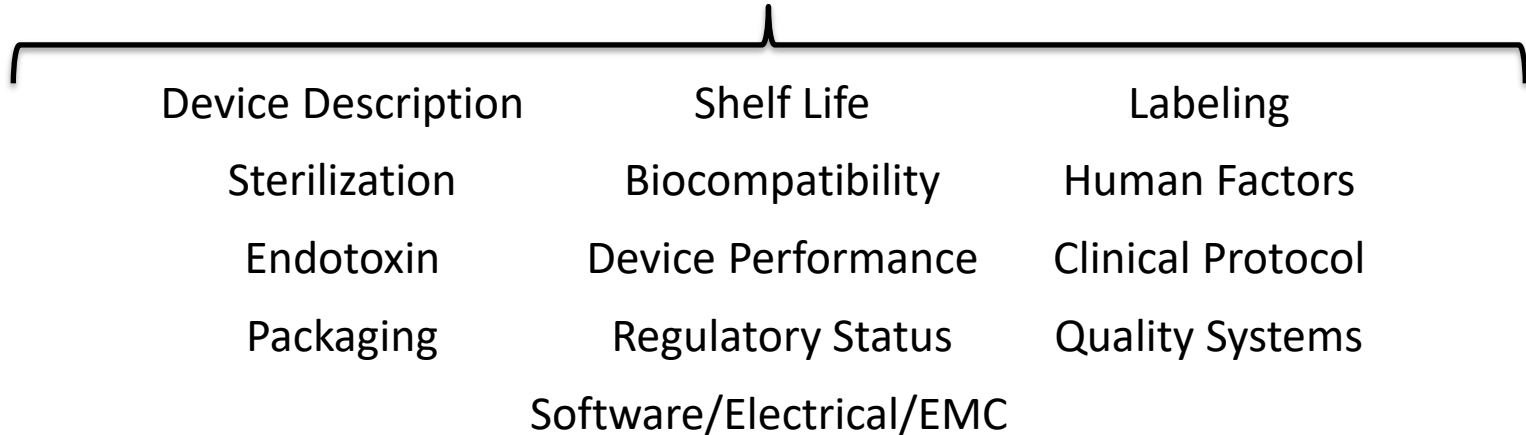
Delivery Device Considerations



- Safety and effectiveness of the delivery device is **critical** for safety and efficacy of the biological product
- Performance requirements for the delivery device determined by the Sponsor
- Submissions should include information on the device(s) used to administer the biological product

Delivery Device Information

Information to assess the safety & effectiveness of
the delivery device



Delivery Device Performance

- Testing to ensure the delivery device meets specified performance/function requirements (design verification) and achieves its user needs and intended use (design validation)
 - Bench testing
 - Pre-clinical animal testing using the same or representative delivery device and procedure
 - Clinical studies in intended population, use environment, etc. (validation)
- Relevant performance metrics should also be included in drug product stability program

Delivery Device Performance

- Important to identify and control the design outputs necessary to deliver the intended drug dose to the intended delivery site, including product preparation and dose delivery initiation, progression, and completion
- Biologic/device compatibility testing
 - Ensure drug product quality and device performance maintained when used together
 - Should use worst case clinical parameters

Delivery Device Regulatory Status



- Proposed device may have been previously cleared (510(k)), classified (De Novo) or approved (PMA, HDE, or with a BLA/NDA))
- May address some safety information (e.g., sterilization, biocompatibility, software, electrical safety, EMC, etc.) if the same or similar:
 - Intended use/indication for use
 - Users and use environment
 - Route of administration (ROA)
 - Contact classification
- Modifications to the device require additional information to address new risks
- Compatibility with the investigational biological product is always needed

REGULATORY SUBMISSIONS AND INTERACTING WITH OTP

Regulatory Submissions

- Device information may be provided in an IND (Section 3.2.R) for investigational biological product or in a Master File (MF or MAF)
- Letter of authorization from MF holder needed
 - Signed/dated and should identify specific information cross referenced and specific location of the information in the MF or MF amendment
- MF holder and authorized cross-referencing party need to communicate
 - MF holder should inform cross referencing biologic sponsor(s)/applicant(s) when changes are made to the device
 - Sponsor/applicant should assess the impact of this change on the delivery of their biologic and submit additional information to FDA

Combination Products

Combination of biologic, drug, and/or device constituents as defined in 21 CFR 3.2(e)

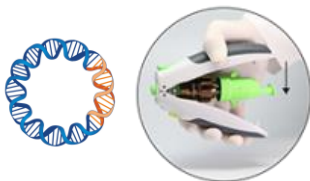
(1) Physically, chemically, or otherwise combined or mixed and produced as a **single entity**



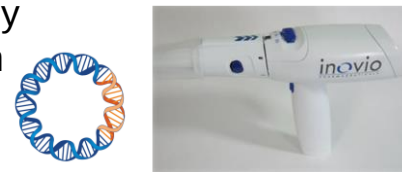
(2) Two or more separate products packaged together in a single package or as a unit (**co-packaged**)



(3) Packaged separately and **cross-labeled** for use only with an *approved product* (approved product labeling must be changed)



(4) Packaged separately and **cross-labeled** with another *investigational product*

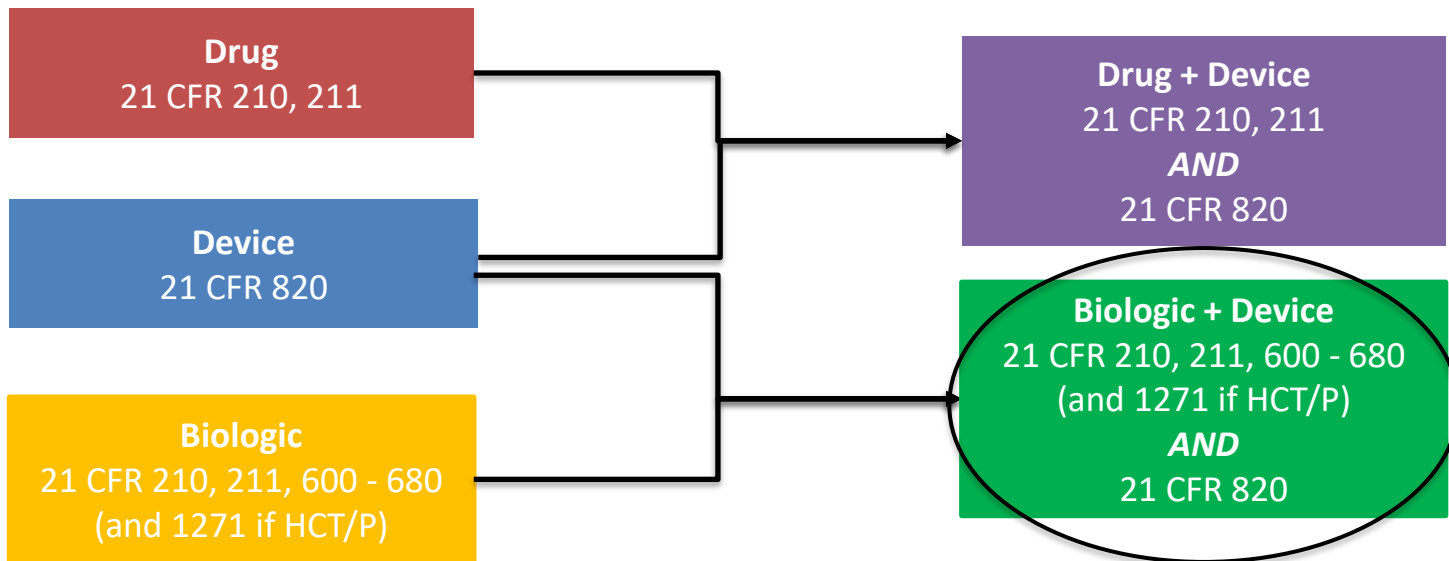


Current Good Manufacturing Practice (cGMP) Requirements



Constituents retain their regulatory status (i.e., as a drug, biologic, or device) when they are combined

Each constituent's respective CGMP requirements apply to the **overall combination product**



Guidance for Industry and
FDA Staff:
Current Good Manufacturing Practice
Requirements for Combination Products
FINAL GUIDANCE

The draft of this document was issued in January 2015.

Additional copies are available from:
Office of Combination Products
Food and Drug Administration
FDA-202, Hatcher Room 60120
10801 New Hampshire Avenue
Silver Spring, MD 20910
(Tel) 301-795-8310
(Fax) 301-847-0819
<http://www.fda.gov/oc/combination>

For questions regarding this document, contact the Office of Combination Products at 301-795-8030 or combination@fda.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Combination Products (OCP) is the Office of the Commissioner
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)
Center for Devices and Radiological Health (CDRH)
Office of Regulatory Affairs (ORA)

January 2017

cGMPs: Streamlined Approach (21 CFR 4.4)



Can meet requirements of both drug CGMPs* and
device quality system regulations (QSR) with a
CGMP operating system that complies with...

* Biologics are also subject to 21 CFR 600 - 680 (and 21 CFR 1271 if biologic is an HCT/P)

<https://www.fda.gov/media/90425/download>

Drug CGMPs and subset of device QSR

- (i) 21 CFR 820.20 Management responsibility
- (ii) 21 CFR 820.30 Design controls
- (iii) 21 CFR 820.50 Purchasing controls
- (iv) 21 CFR 820.100 Corrective and preventive action
- (v) 21 CFR 820.170 Installation
- (vi) 21 CFR 820.200 Servicing

OR

Device QSR and subset of drug CGMPs

- (i) 21 CFR 211.84 Testing and approval or rejection of components, drug product containers, and closures
- (ii) 21 CFR 211.103 Calculation of yield
- (iii) 21 CFR 211.132 Tamper-evident packaging requirements for over-the-counter (OTC) human drug products
- (iv) 21 CFR 211.137 Expiration dating
- (v) 21 CFR 211.165 – 211.167 Testing and release for distribution, stability testing, special testing requirements
- (viii) 21 CFR 211.170 Reserve samples

Guidance for Industry and
FDA Staff:
Current Good Manufacturing Practice
Requirements for Combination Products
FINAL GUIDANCE

The draft of this document was issued in January 2015.

*Additional copies are available from:
Office of Combination Products
Food and Drug Administration
H202, Biobulb Room 62129
10801 New Hampshire Avenue
Silver Spring, MD 20993
(Tel) 301-795-8310
(Fax) 301-847-0819
<http://www.fda.gov/oc/combination>*

For questions regarding this document, contact the Office of Combination Products at 301-795-8030 or combination@fda.gov

U.S. Department of Health and Human Services
Food and Drug Administration
Office of Combination Products (OCP) in the Office of the Commissioner
Center for Biologics Evaluation and Research (CBER)
Center for Drug Evaluation and Research (CDER)
Center for Devices and Radiological Health (CDRH)
Office of Regulatory Affairs (ORA)

January 2017

cGMPs: Streamlined Approach (21 CFR 4.4)



Can meet requirements of both drug CGMPs* and device quality system regulations (QSR) with a CGMP operating system that complies with...

* Biologics are also subject to 21 CFR 600 - 680 (and 21 CFR 1271 if biologic is an HCT/P)

<https://www.fda.gov/media/90425/download>

Drug CGMPs **and** subset of device QSR

(i) 21 CFR 820.20 Management responsibility

(ii) 21 CFR 820.30 Design controls

(iii) 21 CFR 820.50 Purchasing controls

(iv) 21 CFR 820.100 Corrective and preventive action

(v) 21 CFR 820.170 Installation

(vi) 21 CFR 820.200 Servicing

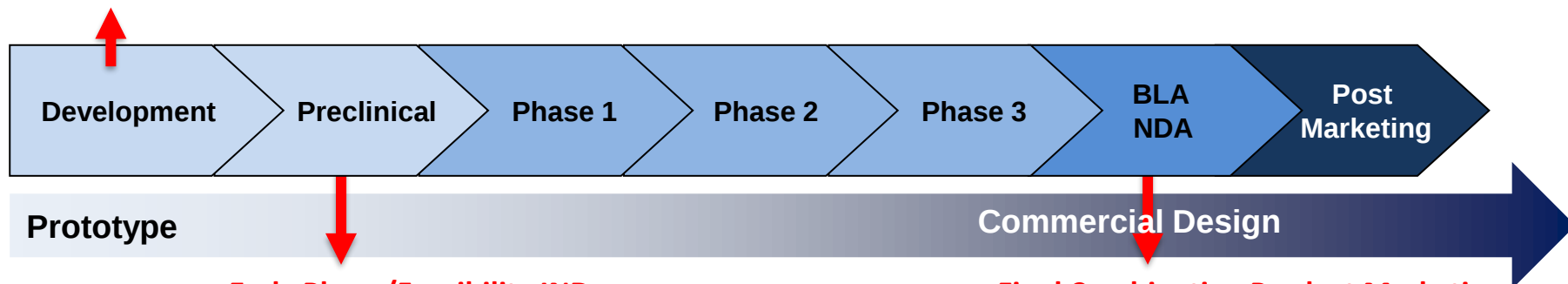
Investigational combination products that include device constituent parts **are subject to design controls** under 21 CFR 820.30 (i.e., during investigational phases)

Pharmaceutical development practices (e.g., ICH Q8/9/10, QTPP, CQAs) can be leveraged and built upon when demonstrating compliance with design controls for a combination product.

Design Controls



Design controls should start as early as possible



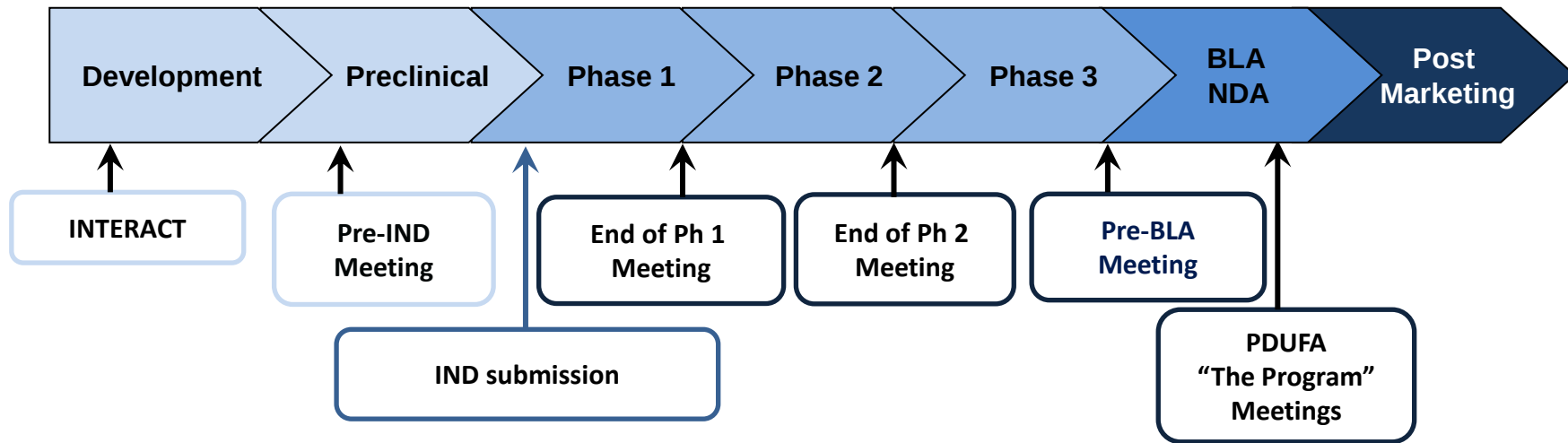
Early Phase/Feasibility IND

- (At minimum) **risk analysis** with **supporting data/information** demonstrating safety risks have been identified and sufficiently mitigated
- Supporting data includes **performance verification data** (e.g., from bench testing, pre-clinical testing) demonstrating investigational product functions as intended

Final Combination Product Marketing Application

- Documentation of design inputs, outputs, verification, validation, risk management (e.g., DHF, RMF)
- Identification, verification, validation of Essential Performance Requirements (EPRs)
- EPR control strategy, EPRs maintained at expiry and after shipping

Interacting with OTP



Summary

- Device design verification and validation is critical for delivery devices used to administer biological products to patients
 - Delivery devices should be compatible with the final biological product
- Delivery device information should be provided in investigational applications for biological products or cross-referenced to Master Files
 - Sponsors using delivery devices to administer cell and gene therapy products are responsible for ensuring delivery devices meet appropriate requirements
- Each constituent's respective cGMP requirements apply to the overall combination product
- Seek FDA advice early and throughout product development

Resources



- 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>
- Combination Products Guidances: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/combination-products-guidance-documents>
- 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>

Contact information

- **Laura Ricles, PhD**
Email: laura.ricles@fda.hhs.gov
- **Regulatory Questions:**
OTP Main Line – 240 402 8190
Email: OTATRPMS@fda.hhs.gov
- **OTAT (OTP) Learn Webinar Series:**
<http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm>
- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm
Phone: 1-800-835-4709 or 240-402-8010
- **Consumer Affairs Branch:** ocod@fda.hhs.gov
- **Manufacturers Assistance and Technical Training Branch:** industry.biologics@fda.gov
- **Follow us on Twitter:** <https://www.twitter.com/fdacber>



FDA Headquarters



