Introduction to Biological Products, Including Vaccines, Cell and Gene Therapies, and Other Advanced Therapies

Regulation of Biological Manufacturing

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Objectives

- Understand the Biologic Manufacturing Process
- Explore the Laws that Control Biologic Products
- Examine the Regulations that Apply to Biologics Manufacturing

The Law and Legislation

- Under section 351(a)(2)(C) of the PHS Act, FDA will approve a biologics license application (BLA) on the basis of a demonstration that the biological product is safe, pure, and potent, *and that the facility in which the biological product is manufactured meets standards designed to assure that the biological product continues to be safe, pure, and potent*.

- Section 351(c) of the PHS Act authorizes FDA to conduct a pre-approval inspection of the facility in which the product is manufactured.

The Law and Legislation

- A manufacturer thus includes a license applicant, who may or may not own the facilities engaged in significant manufacturing steps, when such an applicant assumes responsibility for compliance with the applicable product and establishment standards, including, but not limited to 21 CFR Parts 210, 211, 600 through 680, and 820.

The Law and Regulation

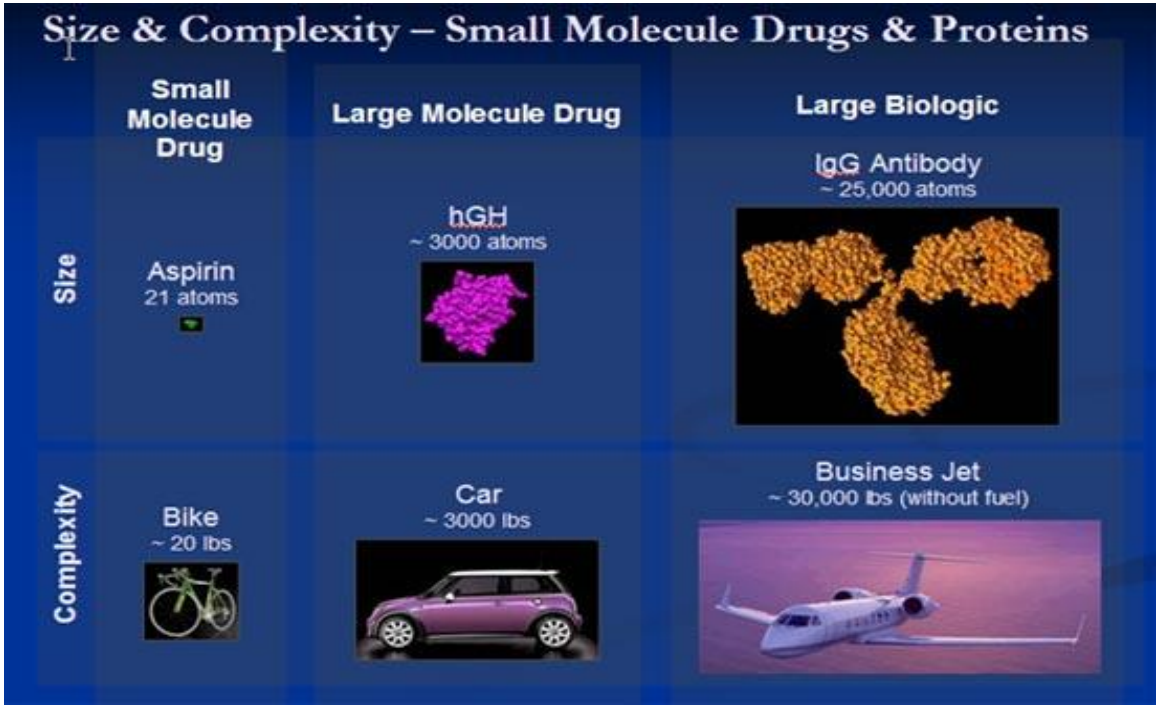
- “Manufacture” is defined as “all steps in propagation or manufacture and preparation of products and includes but is not limited to filling, testing, labeling, packaging, and storage by the manufacturer” (21 CFR 600.3(u)).

- A manufacturer of a biological product must demonstrate responsibility for the manufacturing process as described in its BLA (21 CFR 600.3(t)). For example, a manufacturer must avoid introduction of contaminants during production (21 CFR 610.13).

The Biologic Manufacturing Process

- **Biomanufacturing** is the production of biologic products from living cells such as antibodies and enzyme replacement therapies.
  - Small molecule drugs can be synthesized chemically.
  - As their name suggests, biologics require living cells.

Biologics vs. Small Molecules



Hypothetical Question

- If we have the same facility, using the exact same equipment, with the same personnel, can they produce the exact same biologic product over several batches? 50 batches?
- Why or why not?

The Biologic Manufacturing Process

- **Step 1:** Establish the cell bank / designing a cell to produce a specific protein. The protein is transferred by encoding a gene into the production cell.
  - Production cells can be bacteria, animals or plants.
  - E. Coli and Chinese Hamster Ovaries (CHO) are two common production cells.
  - Once the cell produces the protein, the cells multiply and the genetically identical cells are called the *production cell line*.

The Biologic Manufacturing Process

- **Step 2:** The manufacturer produces a *Master Cell Bank.*
  - The master cell bank supplies genetically identical cells for future products.
  - The cells are transferred to a *Bioreactor.*
  - A growth medium with the proper nutrients, temperature and oxygen for cell growth to occur.

The Biologic Manufacturing Process

- Millions of cells are created.
- Cells are placed in receptacles (vials).
- The vials are frozen with liquid nitrogen (-196°C).
- Freezing stops cell growth.
- Cells are stored in 3 physically different locations.
- The *working cell bank* is created by thawing one vial from the master cell bank and allowing it to multiply for several generations.

The Biologic Manufacturing Process

- Mammalian vs. Bacterial
- Insulin, the first biologic drug, was produced using E. Coli cells.
- Bacteria works for Unicellular organisms, but not multicellular organisms.
- Mammalian needed unfold complex proteins and confer *post translational modifications*.

The Biologic Manufacturing Process

- Certain cells like CHO's have GRAS status by the FDA (Generally Recognized as Safe).
- Cells used to produce the protein must be filtered out.
- Purify Therapeutic Proteins away from the Cellular Proteins.

FDA Regulations Biomanufacturing

- 21 CFR Parts 210, 211, 600 through 680, and 820.
- 21 CFR 210, 211 Current Good Manufacturing Practices for Drugs and Biologics.
- Add § § 600-680 for Biologics.

21 CFR 210-211

A Drug is considered adulterated if:

- contains any filthy or decomposed substance
  - (FDCA §501(a)(1), 21 U.S.C. §351(a)(1));
- prepared, packed or held under unsanitary conditions
  - (FDCA §501(a)(2)(A), 21 U.S.C.§351(a)(2)(A);
- methods or processes used are not in conformance with good manufacturing practices
  - (FDCA §501 (a)(2), 21 U.S.C. §351 (a)(2)(b), 21 CFR Part 210 & 211);

21 CFR 210-211

- container composed of poisonous or deleterious substance may cause contents to be injurious to health
  - (FDCA §501 (a)(3), 21 U.S.C. §351 (a)(3));
- contains an unsafe coloring additive
  - (§501 (a)(4), 21 U.S.C. §351 (a)(4));
- strength, quality or purity falls below compendia standards
  - (§501 (b), 21 U.S.C. §351 (b));
- strength or purity falls below what it purports to possess
  - (§501 (c), 21 U.S.C. §351 (c));
- mixed or packaged to reduce quality or strength
  - (§501 (d), 21 U.S.C. §351 (d));

21 CFR 210-211

- labeling is false or misleading
  - (FDCA §502 a), 21 U.S.C. §352(a));
- label fails to bear the name and place of business, an accurate statement of contents, weight, measure or numerical count
  - (FDCA §502(b), 21 U.S.C. §352(b));
- labeling required is not prominently displayed and understandable
  - (FDCA §502(c), 21 U.S.C. §352(c)).

Good Manufacturing Practices

Must be Current: Issue

- Good manufacturing Practices were implemented by the FDA to ensure that Drug Products are manufactured in an appropriate and safe way.
  - (21 CFR 210 & 211)
- FDCA grants FDA authority to ensure compliance with current GMP.
  - (cGMP) (§ § 301(a), 501(a)(2)(b); 21 USC § § 331(a); 351(a)(2)(b)
- A Drug is adulterated if found not to be manufactured according to cGMP's.
  - (§ § 301(a), 501(a)(2)(b);

Good Manufacturing Practices

- A drug can meet its specifications, contain no detectable impurities, be both safe and effective and still be considered adulterated if the manufacturing was not in compliance with cGMP's.
  - (FDCA §501 (a)(2), 21 U.S.C. §351 (a)(2)(b), 21 CFR Part 210 & 211);
- The role of the FDA is to determine which practices in use are "good" and enforce those.
- FDA does not prescribe "how to make products," but requires manufacturers to do so.
- Must establish: Procedures which assure the drug is manufactured in a way to consistently meet specifications.

Good Manufacturing Practices

Main Concepts:

- Quality, Safety and Effectiveness must be designed and built into a product.
- Quality cannot be inspected or tested into a product (no testing into compliance, Dev or OOS required).
- Each step of the manufacturing process must be controlled to [ensure] the finished product will be acceptable.

Good Manufacturing Practices

GMP's: Ten (10) Sections:

- Organization and Personnel
- Buildings and Facilities
- Equipment
- Components, Drug Product Containers, and Closures
- Production and Process Control

Good Manufacturing Practices

Production Process and Controls:

- Requires written procedures (SOP's and validation) to conduct batch production and processing in a way ensuring the accuracy of:
  - Identity
  - Strength
  - Purity
  - Quality
    - (21 CFR 211(f))

Good Manufacturing Practices

- These written procedures, including any changes, shall be drafted, reviewed, and approved by the appropriate organizational units and reviewed and approved by the quality control unit.
- Written production and process control procedures shall be followed in the execution of the various production and process control functions and shall be documented at the time of performance.
- Any deviation from the written procedures shall be recorded and justified. 21 CFR 211.100

Testing and Release for Distribution

211.165 Testing and release for distribution.

- For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release.
- **Process**
  - Process validation for drugs (finished pharmaceuticals and components) is a legally enforceable requirement under section 501(a)(2)(B) of the Act (21 U.S.C. 351(a)(2)(B)).

Good Manufacturing Practices in Enforcement

- FDA must only prove:
  - Manufacturer did not follow a particular practice
  - Practice was deemed “Good” by FDA
- Cases:
  - Provide flexibility…specific enough to assure drug is safe and reliable…
    - » *U.S. v. Bel Mar Labs*, 284 F. Supp. 875

GMP Documentation

- CGMP documents for commercial manufacturing (i.e., the initial commercial master batch production and control record (§ 211.186) and supporting procedures) are key outputs of Stage 1.
- Documentation requirements are greatest during Stage 2, process qualification, and Stage 3, continued process verification.

Inspections

- Reasonableness of the Inspection (time, limits, manner) § 704
- Frequency of Inspections 21 U.S.C. §360(h)
- No Consent is Required (Pervasively and Extensively regulated industry)
- No Search Warrant is Required
- Miranda Warnings do not apply unless criminal investigation is opened (none for Inspection and evidence admissible criminally)
- Administration Inspection Warrants

FDA Inspection Legalities

FDA Entitled to:

- Relevant information concerning whether drugs (for human consumption) are:
  - Manufactured
  - Transported
  - Processed
  - Packed
- In accordance with the Act [FDCA]
  - (704(a)(1); 21 USC 374(a)(1)

FDA Inspection Legalities

NOT Entitled to:

- Financial data
- Sales data (other than shipping amounts)
- Pricing data
- Personnel data (other than the qualifications of professional personnel)
- Research data (except for data required to be disclosed under 21 USC 374 ‘approval data’)
- Internal audit, supplier audit, mgmt. reviews)

21 CFR 600-680 Regs

- For Biologics 21 CFR 600-680 Regulations apply on top of 21 CFR 210-211
- Demonstrate biological product is safe, pure, and potent
- Section 610 Standards for Biologic Products

Products Governed by 600-680

- Vaccines;
- Allergenic products;
- Plasma-derived products e.g., albumin, immunoglobulins, clotting factors, fibrin sealants, proteinase inhibitors, etc.); and their recombinant analogs;
- Antitoxins, antivenins, and venoms;
- Naturally-derived (i.e., not recombinant) protein products (e.g., naturally-derived enzymes and certain toxins);
- Cellular and gene therapy products;
- In vitro diagnostics (IVDs) regulated under the PHS Act (e.g., blood donor screening assays, etc.); and
- Other biological products licensed under the PHS Act.

600 Sections and the Act

- In addition, section 506A of the FD&C Act (21 U.S.C. 356a) provides requirements for making and reporting manufacturing changes to an approved BLA and for distributing a licensed product made with such a change.

21 CFR 600 General

- Mailing Addresses
- Establishment Standards and Personnel
- Physical Establishment/Equipment
- Records
- Retention Samples
- Distribution Reports
- Agency Notifications

21 CFR 610

- Subpart A - Release Requirements
- § 610.1 Tests prior to release required for each lot
- Subpart B - General Provisions
- § 610.9 Equivalent methods and processes
- § 610.10 Potency
- § 610.12 Sterility
- § 610.13 Purity
- § 610.14 Identity

21 CFR 610 Standards

- § 610.16 Total solids in serums
- § 610.17 Permissible combinations
- § 610.18 Cultures
- § 610.44 Use of reference panels by manufacturers of test kits
- Testing for HIV, Hep C, etc.
- Longevity---product dating
- Package Label Requirements