Biologics Regulatory Framework
Statutory Framework for Biologics

**Drugs**
- Investigational Use Application
  - IND
- Pre-Market Approval Applications
  - §505(b)(1) NDA
  - §505(b)(2) NDA
  - §505(j) ANDA
- Over-the-Counter (OTC) Non-Rx Drugs
  - Monograph

**Biologics**
- Investigational Use Application
  - IND
- Pre-Market Approval Applications
  - §351(a) BLA (PHSA)
  - §351(k)(2)(A) Biosimilar
  - §351(k)(2)(B) Interchangeable Biosimilar
Biologics vs. Drugs

- Distinctions between chemical and biological pharmaceuticals
  - Chemical
    - Small molecule
    - Synthesized in vitro by chemical process
    - Purification and characterization straightforward
  - Biologics
    - Large molecule
    - Produced in vivo (in biological system)
    - Characterization and purity ongoing challenge
    - Manufacturing process determines safety, purity, and potency
Biologics Review Since 2003

CDER

- Proteins for therapeutic use
  - Cytokines, enzymes;
- Monoclonal antibodies
- Immunomodulators
- Growth factors intended to mobilize production of cells in vivo.

CBER

- Vaccines
  - Intended to enhance immune response
- Blood Products
- Tissues
- Gene Therapy Products
- Antitoxins, antivenins, venoms
- Allergenic extracts

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§351(a) Biologics License Application (BLA)

- §351 of the Public Health Service Act (PHSA):
  - "(a) (1) No person shall introduce or deliver for introduction into interstate commerce any biological product unless –
    - (A) a biologics license is in effect for the biological product; and
    - (B) each package of the biological product is plainly marked [with proper name, manufacturer information, and expiration date]
§351(a) BLA

§351(a) Biologics License Application (BLA)
- Analogous to 505(b)(1) NDA for drugs
- “Soup to Nuts” approach
- Prior to 2009, there was no abbreviated approval pathway for products licensed under 351 of the PHSA until 2010
- Generally, same content and format as required for the 505(b)(1) NDA, however, greater emphasis on CMC content and evaluation ("product is the process mentality")
BPCI Act of 2009

- Biologics Price Competition and Innovation Act of 2009
  - Signed into law on 3/23/10
  - Intent of the statute similar to Hatch-Waxman Amendments to FD&C Act
  - aligns with the FDA’s longstanding policy of permitting appropriate reliance on what is already known about a drug, thereby saving time and resources and avoiding unnecessary duplication of human or animal testing.
  - Balances additional incentives to innovate and price competition
  - Created abbreviated approval pathway for biologics.

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§351(k) Abbreviated Applications

§351(k) “Abbreviated” Application

- BPCI added two subsections, (k)(1) and (k)(2) that deal with two distinct thresholds for comparing the innovator product to an abbreviated applicant:
  - Bioimilarity or
  - Interchangeability
§351(k)(1) Biosimilar BLA

“Biosimilar”

“highly similar to the reference product notwithstanding minor differences in clinically inactive components” and “there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency.” (351(i) of the PHSA)

Not “generics” like 505(b)(1) because the active ingredients are not the same, but merely similar.

FDA approved first biosimilar product on 3/6/15 (Sandoz Inc’s Zarixo is biosimilar to Amgen Inc.’s Neupogen as treatment for patients receiving forms of chemotherapy).
§351(k)(1) Biosimilar BLA

“Biosimilar” (continued)

- Biosimilarity based on:
  - Analytical studies showing highly similar;
  - Animal studies, including toxicology; and
  - Clinical studies or studies demonstrating safety, purity and potency in a condition of use for which reference product is licensed

- Biosimilar and Reference Product:
  - Share same mechanism of action for intended use
  - Condition(s) of use same as those approved for reference product
  - Same route of administration, dosage form, and strength

- Facility meets standards designed to ensure safe, pure, and potent product.
§351(k)(2) Interchangeable BLA

- Interchangeable
  - Meets the standards in subsection 351(k)(4) and biological product may be substituted for the reference product without the intervention of the healthcare provider who prescribed the reference product.” (351(i)(3))
  - 351(k)(4) requirements
    - “Biosimilarity” and
    - “can be expected to produce the same clinical results as the reference product in any given patient” and
  - No additional risk of switching between reference and interchangeable product
- Most heated dispute on this issue.
- No Interchangeable BLAs approved to date.
Biosimilar Guidance (2012)

- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product
  - Risk-based, totality-of-the evidence approach to evaluate Biosimilarity to a reference product

- Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product
  - Overview of analytical factors to consider when assessing Biosimilarity, including analytical, physicochemical and biological characterization

  - Exclusivity questions, formulation changes, manufacturing changes
Vaccine Regulation

- Regulated by CBER’s Office of Vaccines Research and Review (OVRR)
- 351 BLA
  - Pre-IND GLP Animal Studies
  - Requires thorough review of laboratory and clinical data to ensure the safety, efficacy, purity and potency of these products.
  - IND required
- Similar 3-Phase Trial Framework
  - Immunogenicity, facility inspection, lot release (Phase 4)
Vaccine Regulation

- CMC Content more complex
  - Origin, collection, manipulation, source material, purification
  - Genetic material, modification, purification
  - Evaluation/risk-assessment of patent cells (screen donors)
  - Testing for viruses – donors, animals, host cells, cell banks
  - Controls re: cell banks, sentinel animals,

- cGMPs apply here (21 CFR 210, 211); greater emphasis on process validation
Vaccine Efficacy

3 Ways to show vaccine efficacy:

- Clinical Endpoint
  - Primary clinical endpoint is the treatment or prevention of disease
  - Prospective, controlled, randomized trials
  - Recall 1998 Efficacy Guidance

- Immune Response Endpoints (if accepted by FDA)
  - Correlate of protection shown where a laboratory parameter is associated with the protection from clinical disease
  - Most useful where there is a clear qualitative and quantitative relationship between the correlate and the clinical disease

- Animal Rule
  - 21 CFR Subpart I
Animal Rule

“Subpart I” 21 CFR 314.600, 601.90 et seq.)

- applies to new drug and biologics that are intended to treat or “prevent serious or life threatening conditions causes by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances” and where “human efficacy studies cannot be conducted because it would be unethical….and field trials…have not been feasible.” 21 CFR 314.600
- FDA will rely on animal studies to show efficacy when, inter-alia, :
  - Effect is demonstrated in more than 1 animal species that represents a well-characterized animal model for predicting the response in humans;
  - Animal study endpoint is related to the desired endpoint in humans, generally improved survival or prevention of major morbidity;
  - Selection of an effective dose is supported by the evidence. See 21 CFR 314.610(a)(1)-(4).
Animal Rule

- Subpart I” 21 CFR 314.600, 601.90 et seq.) (cont.)
  - Post-market studies when exigency emerges. See 21 CFR 610.(b)(1)
  - Restricted distribution required. See 21 CFR 610.(b)(2)
  - Animal Rule studies must be GLP compliance (21 CFR 58)
  - See New Drug and Biological Products; Evidence Needed to Demonstrate Efficacy of New Drugs When Efficacy Studies are Not Ethical or Feasible. 21 CFR 601.90-95, 21 CFR 314.600-650; FR 67:37988 98; May 31, 2002.
Stages of Vaccine Development

Phase 1
Safety
Immunogenicity

Phase 2
Safety
Immunogenicity
Efficacy
Dose-Ranging

Phase 3
Safety
Immunogenicity
Efficacy

BLA Submission
Data to support safety, purity and potency determination and facility inspection

Clinical Studies Completed Under IND

BLA Supplement
Safety
Immunogenicity
Efficacy

Phase 4/ Post-marketing
Inspection
Lot Release
Safety
Efficacy
HCT/Ps

- Human cell, tissue, cellular and tissue-based products (HCT/Ps)
  - Human cells or tissues intended for implantation, transplantation, or infusion in a human recipient. (21 CFR 1271.3(d))

- Regulation of HCT/Ps is based on risk to the recipient:
  - Low risk: regulated under §361 of the PHSA and requires no pre-marked review
  - High risk: regulated under 351 of the PHSA and requires pre-market review of a BLA
HCT/Ps

HCT/P is a “361 HCT/P” if it meets the following risk-based criteria at 21 CFR §1271.10(a):

- HCT/P is minimally manipulated;
- HCT/P is for homologous use as reflect by objective intent;
- is not combined with another article except water, sterilizing and preserving solution and such agents do not raise new clinical safety concerns with respect to HCT/P and
- either
  - (i) no systemic effect and not dependent on metabolic activity or
  - (ii) systemic effect and dependent on metabolic activity, but for autologous use.
HCT/Ps

- 21 CFR 1270 and 1271 require tissue establishments to screen and test donors, to prepare and follow written procedures for the prevention of the spread of communicable disease, and to maintain records.
- Tissue Establishment and Registration (Form 3356) required
- Current Good Tissue Practices (cGTPs)
  - 21 CFR part 1271.145-320 (Subpart D): personnel, procedures, facilities, processing and controls, equipment, recovery, record-keeping, etc.
Blood Regulation

- CBER is responsible for regulatory oversight of the U.S. blood supply.
- FDA enforces standards for blood collection and for the manufacturing of blood products, including both transfusible components of whole blood, pharmaceuticals derived from blood cells or plasma
- FDA also inspects blood establishments and monitors reports of errors, accidents and adverse clinical events
Blood Regulation

- 5 Layers of Blood Regulation
  - Donor Screening
  - Blood Testing
  - Donor Lists
  - Quarantine
  - Problems and deficiencies addressed

- cGMPs apply (21 CFR 210, 211, 606)

- Registration and Listing required.