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

March 16-17, 2022 | Virtual Event

Preconference Primer I. Overview of FDA and Regulatory Processes
(60 Minute Prerecording)

Learning Objectives

- Learn about the role of the Food and Drug Administration (FDA) and the U.S. Department of Health and Human Services (HHS) in the regulation of medical products, including biological products, drugs, and devices
- Identify and become familiar with key aspects of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the Public Health Service Act (PHSA) that authorize FDA to make regulatory decisions, issue regulations and guidances, and develop regulatory policy for medical products, and how stakeholders can participate in these activities
- Learn about FDA's responsibilities under the Freedom of Information Act, and about the Agency's duty to safeguard confidential commercial information, trade secrets, and other information.

Steven S. Tjoe, Senior Associate, Goodwin Procter LLP

A. Food and Drug Administration

1. Role in the Federal Government
    a. Part of HHS where sister agencies include
        i. Center for Medicare and Medicaid Services (CMS)
        ii. HHS Office of Inspector General (OIG)
        iii. National Institutes of Health (NIH)
        iv. Centers for Disease Control and Prevention (CDC)
    b. Succeeded NIH as agency responsible for regulating biological products
2. FDA Mission
3. FDA Structure
    a. Centers
        i. Both the Center for Biologics Evaluation and Research (CBER) and the Center for Drug Evaluation and Research (CDER) regulate biological products
        ii. The Center for Devices and Radiological Health, regulates the great majority medical devices, CBER is responsible for certain medical devices including certain in vitro diagnostic products (IVDs)

4. Headquarters and the Field

B. FDA Law and Policies

1. Statutes: Federal Food, Drug, and Cosmetic Act of 1938 (FDCA) and Public Health Service Act of 1944 (PHSA)
2. Regulations
    a. Federal Register Notices
    b. Code of Federal Regulations (CFR)
3. Guidance Documents/Compliance Policy Guides (CPGs)
    a. Good Guidance Practices (GGP)
    b. Advisory opinions and Preambles
    c. Staff manuals, guides and programs
4. Enforcement actions and letters
    a. Citizen Petition responses
    b. Informal statements and advice

C. Participating in FDA Policy Making

1. Comments on proposed regulations and draft guidance
2. FDA meetings and workshops
3. Advisory committee meetings
4. Citizen Petitions
5. Prescription Drug User Fee Act (PDUFA) and Biosimilar User Fee Act (BsUFA) negotiations
6. Lobbying Congress
7. Judicial review

D. Product Specific Proceedings

1. Dispute resolution, appeals
2. Ombudsman
3. Citizen Petitions
4. Regulatory Hearings
5. Formal adjudications
6. Judicial review

E. Obtaining and Protecting Information under the Freedom of Information Act (FOIA)

1. Information held by FDA is disclosable under FOIA under an exemption applies
2. Nine exemptions from mandatory disclosure
    a. Focus on trade secrets/commercial/financial information that is confidential or privileged
    b. Disclosure prohibited by another federal law
    c. Privileged communication between agencies
3. Discretionary disclosure on request
4. Preventing disclosure of information submitted to FDA
    a. Pre-submission review by FDA
    b. Right to notice of proposed disclosure
    c. Reverse FOIA litigation

Wednesday, March 16

11:00 AM **FDLI Welcome and Announcements**
Khara L. Minter, Assistant Director, Training Programs, FDLI

11:05 AM–12:20 PM II. Introduction to FDA Review and Approval of Biological Products

Learning Objectives

- Learn the statutory definitions of a biological product as well as recognize the distinctions that drive jurisdiction and regulatory pathways
- Understand pathways to market and how to determine which pathway to choose
- Understand the applicability of both the PHS Act and the FDCA to biological products

Catherine M. Cook, Principal for Regulatory Policy, Greenleaf Health, Inc.

A. The Statutory Framework for Biologics

1. The 1902 Biologics Act
2. Federal Food, Drug, Cosmetic Act of 1938 (FDCA)
3. Public Health Service Act of 1944 (PHS Act)
4. Significant Amendments of the FDCA and PHS Act include:
    a. Prescription Drug User Act (PDUFA) and Biosimilar User Fee Act (BsUFA) (and reauthorizations)
    b. The Food and Drug Modernization Act of 1997 (FDAMA)
    c. Food and Drug Administration Amendments Act of 2007 (FDAAA)
    d. Biologics Price Competition and Innovations Act (BPCIA)
    e. Food and Drug Administration Safety and Innovation Act (FDASIA)
    f. 21st Century Cures Act

B. Basic Principles

1. Definitions drive jurisdiction and pathway
    a. Biological Product means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein, or analogous, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings.
    b. "Drug" defined in 21 USC 321(g)(1)
        i. A key principle: Intended use
    c. "Device" defined in 21 USC 321(h)
        i. Key limitations: does not achieve its primary intended purposes through chemical action within or on the human body and not dependent upon being metabolized
2. Discuss:
    a. Biological Product vs. Drug
    b. Biological Product vs. Medical Device

c. Biological Product vs. Veterinary Biologic
d. Biological Product vs. Cosmetic
e. Biological Product vs. Food, Dietary Supplement

C. Different Pathways to Market for Biological Products, Drugs, and Devices

1. Biologics License Application (BLA)
   a. Full BLA – 351 (a) application
   b. (Biosimilar) – 351 (k) application
2. New Drug Application (NDA)
   a. Full NDA
   b. Abbreviated NDA
   c. 505(b)(2) Application
3. Device Applications/Notifications
   a. PMA
   b. 510(k)
   c. Exempt products

D. Combination Products

1. Regulations and Policies
   a. Product jurisdiction and classification
   b. Primary Mode of Action (PMOA)
   c. Current Good Manufacturing Practices for Combination Products
   d. Post Market Safety Reporting for Combination Products
   e. CDER, CBER, and CDRH Intercenter Agreements

12:20–12:30 PM Break

12:30–1:45 PM III. Regulation of Biological Product/Development

Learning Objectives

- Summarize preclinical and clinical testing, sources of Good Clinical Practice (GCP) requirements and phases of the clinical trial process
- Identify the obligations of sponsors and investigators
- Learn about interacting with FDA during product development
- Understand compliance and enforcement considerations for development programs

Christopher M. Mikson, Partner, DLA Piper LLP

A. Preclinical Testing

1. Good Laboratory Practices (GLPs) Regulations

B. Clinical Testing

1. Investigational New Drug (IND) Application
2. Good Clinical Practices
3. Clinical Trials
   a. Phase I, II, III

b. Recruitment and enrollment of underrepresented sexes, race/minority groups
    i. 21 CFR 312.42(b)(5)
    ii. FDASIA Section 907
4. Pediatric Trials
    a. Required Pediatric Trials (Pediatric Research Equity Act (PREA))
    b. Pediatric Studies Performed Under Written Request; Pediatric Exclusivity (Best Pharmaceuticals for Children Act (BPCA))
    c. Clinical Trials Conducted Outside of the United States

C. Obligations of Sponsors (#1-#7 may be transferred to a Contract Research Organization)

1. Selecting, obtaining information from, and informing investigators
2. Monitoring
3. Follow investigational plan
4. Identify and inform about new adverse effects/risks
5. Record keeping
6. Reporting
7. Inspections
8. Obtaining financial disclosures from investigators
9. Providing information to clinicaltrials.gov

D. Obligations of Investigators

1. Follow investigational plan
2. Protect rights, safety, and welfare of subjects
3. Obtain informed consent from subjects
4. Control of investigational drugs
5. Recordkeeping
6. Reporting
7. IRB Review
8. Inspections
9. Subject to clinical investigator disqualification

E. Interactions with FDA on Biological Product Development Programs

1. PDUFA Meetings
2. Initial Targeted Engagement for Regulatory Advice on CBER Products (INTERACT) Meetings
3. CBER Advance Technology Team (CATT) Meetings

F. Expedited Programs and Designations

1. Orphan Drug
2. Fast track
3. Breakthrough therapy
4. Accelerated Approval
5. Priority Review
6. Regenerative Medicine Advance Therapy (RMAT)
    i. RMAT Designation vs. Break Through Therapy
    ii. Designation

iii. Accelerated Approval – specific provisions for RMAT products
iv. Benefits and Limitations of RMAT designation

G. Compliance and Enforcement Considerations

1. Clinical holds
2. Promotion of investigational drugs
3. Charging for investigational drugs
4. SEC considerations and interactions
5. Compliance programs
6. clinicaltrials.gov and results database

H. Expanded Access

1. Individual patients, including emergency use
2. Intermediate–size patient populations
3. Treatment IND or treatment protocol (widespread)

1:45–1:55 PM Break

1:55–3:10 PM IV. Human Cellular and Tissue-Based Products (HCT/P), Cell Therapy and Gene Therapy

Learning Objectives

- Learn the definition of human cellular and tissue-based products (HCT/P) and how to determine whether an HCT/P is regulated solely under regulations issued under Section 361 of the PHS Act
- Learn about types of emerging technologies such as cell and gene therapies

Gail Javitt, Partner, Hyman, Phelps & McNamara, PC

A. HCT/P's – Human Cellular and Tissue Based Products

1. PHS Act Section 361, 42 USC 264
   a. Authority to issue regulations to prevent transmissions of communicable disease
   b. Louisiana v. Matthews, 427 F. Supp. 174 (E.D. La. 1977)
   c. Preemption provision
2. What are the Section 361 Regulations for HCT/Ps?
3. HCT/P Definition
4. Criteria for Regulation Solely under Section 361 of PHS Act
   a. Who is responsible for deciding if the criteria are met?
   b. What if a product does not meet these criteria?
5. Criteria for Exemption from 21 CFR Part 1271

B. Cell and Gene Therapies

Cellular therapy products include cellular immunotherapies, cancer vaccines, and other types of autologous and allogeneic cells for certain therapeutic indications, including hematopoietic stem cells and adult and

embryonic stem cells. Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use.

1. Cell Therapies, including stem cell therapies
    i. Definitions of products
    ii. Applications of 21 CFR Part 1271 and, exemption from those regulations
    iii. Cellular product eligibility for regulation
2. Gene Therapies
    i. Mechanisms of action
    ii. Types of gene therapy products:
        - Plasmid DNA
        - Viral vectors
        - Bacterial vectors
        - Human gene editing technology
        - Patient-derived cellular gene therapy products
    iii. Under a dozen approved gene therapies, but the number of open INDs approaches 1,000
    iv. Orphan Drug Issues for Gene Therapies
    v. Gene Therapy "Platforms"
    vi. The Bespoke Gene Therapy Consortium
3. A product may be both a cell therapy and a gene therapy

3:10–3:20 PM Break

3:20–4:35 PM V. Biological Product Approval, Vaccines, Emergency Use Authorization

Learning Objectives

- Learn about the Biologics License Application (BLA) and how it differs from Emergency Use Authorization
- Understand FDA's review and decision process
- Learn the fundamentals of vaccine regulation and how it's regulated by FDA's Center for Biologics Evaluation and Research (CBER)
- Understand the different pathways to market

Christina M. Markus, Partner, King & Spalding LLP

Eva Temkin, Partner, King & Spalding LLP

A. BLA Content and Organization

1. FDA Form 356h and the Common Technical Document
2. Contents
    i. Safety and effectiveness data
    ii. Manufacturing facilities, processes, and controls
    iii. Packaging
    iv. Proposed labeling
    v. Master Files
    vi. Debarment Certification

vii. Clinical Trial Databank Compliance Certification

B. FDA Review of BLAs

1. User Fees
    a. Performance goals
    b. Review clock
2. Advisory Committees
3. Pre-Approval Inspections (PAIs)

C. Approval Standard

1. Safe, pure, and potent
    a. FDA: Potency includes evidence of effectiveness
    b. Substantial Equivalence (SE)
2. Clinical Evidence
    a. Real world evidence
    b. FDA expectations for gathering safety/efficacy data in diverse populations
    c. History of Racial Inequalities in Clinical Trials

D. FDA's Decision

1. Complete response letters
    a. Subject to Appeal/Dispute Resolution
2. Post-market Requirements and Commitments
    a. Post-market studies and clinical trials
    b. Risk Evaluation and Mitigation Strategies (REMS)

E. Vaccines: License Approval with Emergency Use Authorization

1. Types of Vaccines
    a. For childhood diseases
    b. For disease affecting broad populations
    c. For older adults
    d. Flu vaccines
    e. COVID vaccines, including new technology (mRNA vaccines)
2. Risk-Benefit Assessment
    a. Products intended to be administered to a healthy population
    b. Require large clinical trials in diverse populations
3. Role of Advisory Committees
    a. Vaccines and Related Biological Product Advisory Committee (VRBPAC)
    b. CDC Advisory Committee on Immunization Practices (ACIP)
4. Approval and Authorization
    a. BLA Approval
    b. Emergency Use Authorization (EUA)
        i. October 2020 "Emergency Use Authorization for Vaccines to Prevent COVID-19" Guidance
        ii. Relationship Between Vaccine EUA and future BLA Licensing
5. Programs for Vaccine Injuries
    a. For approved vaccines, National Vaccine Injury Compensation Act

   b. For vaccines distributed under EUA, the Public Readiness and Emergency Preparedness (PREP) Act provides targeted liability immunity to covered entities for measures taken in relation to certain countermeasures during a public health emergency. The Countermeasures Injury Compensation Program (CICP) may help pay for costs of medical care and other specific expenses for certain people who have been seriously injured by certain medicines or vaccines.
6. Post-Approval Pharmacovigilance
   a. Long-Term Immunity
   b. Post-Marketing Safety Studies
   c. Adverse Event Reporting in VAERS

Thursday, March 17

11:00 AM **FDLI Welcome and Announcements**
Khara L. Minter, Assistant Director, Training Programs, FDLI

11:05 AM–12:20 PM **VI. Biosimilar Biological Products**

Learning Objectives

- Understand background and definitions of biologic and biosimilar drugs and new drug applications (NDAs) and biologics license applications (BLAs)
- Summarize biosimilar pathways to market and application contents
- Learn about the types of meetings available to interact with FDA
- Examine interchangeability standards and conditions of use

Michelle Divelbiss, Associate, Covington & Burling LLP

A. Important Concepts

1. Reference product
2. "Evergreening"
3. Reference product exclusivity and "umbrella" exclusivity
4. Biosimilar biologics
5. Interchangeable biosimilar biologics
6. "Transition" biologics

B. Biosimilar Pathway to Market

1. Approval Standard
    a. Biosimilar
    b. Interchangeable
2. Application contents
    a. Demonstrating biosimilarity: The pyramid of evidence, with analytical characterization at the base
    b. Additional evidence to demonstrate interchangeability
    c. Use of foreign comparator products
    d. FDA guidance discussing insulin applications
    e. Naming issues
        i. Proper Names Suffixes
        ii. Trade Names

C. Interacting with FDA

1. Biosimilar Product Development program meetings
2. User fees

D. Scope of Approval

1. Conditions of use
2. Labeling and "Skinny" labels with carve-outs
    a. Induced infringement under *GlaxoSmithKlineLLC v. Teva Pharm. USA, Inc., 976 F.3d 1347 (Fed. Cir. 2020)*

3. Post-market labeling changes
4. Pharmacovigilance
5. REMS
6. Pediatric assessments

E. Interchangeable Biological Products

1. State laws permitting pharmacy substitution
2. Interchangeable product exclusivity

F. Timing Issues

1. Submission under 351(k)
2. Approval under 351(k)
3. Patent Resolution Framework
    a. Overview of framework
    b. Notice of commercial marketing
    c. Use of post-grant and inter partes review

12:20–12:30 PM Break

12:30–1:15 PM VII. Post-Approval Pharmacovigilance

Learning Objectives

- Learn the regulatory basis of post-marketing adverse event reporting and become familiar with how CBER conducts these activities, including active and passive surveillance
- Recognize the regulatory basis of post-marketing commitments and requirements, risk evaluation and mitigation strategies (REMS), and understand how CBER implements these tools to enhance post-licensure safety of biologics

Abeba Habtemariam, Counsel, Arnold & Porter LLP

A. Safety and reporting of adverse events

1. Safety reporting obligations
    a. FDA Adverse Event Reporting (FAERS)
    b. Vaccine Adverse Event Reporting (VAERS)
2. Office of Surveillance and Epidemiology
3. Sentinel Initiative

B. Risk Assessment and Risk Management

1. Overview of REMS authorities
2. New safety information
3. FDA's authority to require post-market studies or trials

1:15–1:25 PM Break

1:25–2:25 PM VIII. Regulation of Biological Manufacturing

Learning Objectives

- Examine requirements for establishment registration and listing
- Learn about inspection requirements
- Recognize FDA's inspection authority and its enforcement process

Neil Di Spirito, Partner, Brown Rudnick LLP

A. Establishment Registration and Listing

1. Statutory and Regulatory Provisions

B. Inspections

1. Statutory and Regulatory Provisions

C. Scope of Pre-Approval Inspections (PAIs)

1. Clinical data
2. Current Good Manufacturing Practices (cGMPs) including
    a. Manufacturing in accordance with processes described in the BLA
    b. Packaging
    c. Validation

D. Inspections

1. Audit process
2. Arranged in advance
3. Usually Multi-day
4. Inspection team
5. Search warrants
    a. Administrative
    b. Criminal
6. Procedure
7. Photographs and recordings

E. Responding to FDA Form 483 Observations

F. Post-Approval Manufacturing Issues

1. Manufacturing Changes and Comparability Protocols
2. Biological Products Deviation Reports (and how they differ from Field Alert Reports for drugs)

2:25–2:35 PM Break

2:35–3:35 PM IX. Regulation of Biological Product Marketing

Learning Objectives

- Learn the legal and regulatory requirements surrounding communications about biologics and biosimilars
- Define misbranding, label and labeling, and off-label promotion
- Identify the basic rules for advertising and promotion

Sarah Blankstein, Associate, Ropes & Gray LLP

A. FDA Offices

1. Advertising and Promotional Labelling Branch, Office of Compliance and Biologics Quality (OCBQ), CBER
2. Office of Prescription Drug Promotion (OPDP), Office of Medical Policy, CDER

B. Misbranding

1. Label and Labeling Defined
2. False or Misleading Labeling
    a. Material omissions
3. Off-Label Promotion
    a. Intended use doctrine
    b. Lack of adequate directions for use
4. Statements of identity, source, ingredients, or quantity
5. Danger to health when used according to labeling

C. Advertising and Promotion – General Rules

1. Promotional Labeling
    a. Distinguished from advertisements
    b. Required elements
    c. Prohibited elements
2. Advertisements
    a. Required elements
    b. Prohibited elements
3. Direct-to-Consumer (DTC) Advertisements
4. Advisory review
5. Preclearance for certain products

D. Advertising and Promotion - Biosimilars

1. Label and Labeling
2. Differences from reference product labeling
3. Scope of advertising and promotion based on labeling
4. Comparative claims

E. Other Discussion of Regulated Products

1. Scientific and educational activities
2. Press releases
3. Responses to unsolicited requests

4. Dissemination of information on off-label uses
5. Recent Cases: First Amendment Considerations

3:35–3:45 PM Break

3:45–5:00 PM X. Violations, Enforcement, and International Issues

Learning Objectives

- Learn FDA's enforcement tools and procedures and the factors FDA weighs when making enforcement decisions
- Identify prohibited acts of adulteration and misbranding
- Understand international harmonization and import and export regulations

Brian J. Malkin, Partner, McDermott Will & Emery

A. Interstate Commerce Element

1. Under the FD&C Act
2. Under the PHS Act, including sections 361 (42 USC 264) and 368 (42 USC 371)

B. Prohibited Acts

1. Adulteration (examples, not comprehensive list)
    a. Insanitary conditions
    b. Non-Compliance with cGMP
    c. Deviation from represented compendial standards
    d. Refusal to permit inspection
2. Misbranding (examples, not comprehensive list)
    a. Label and Labeling Defined
    b. False or Misleading Labeling
        i. Material omissions
    c. Off-Label Promotion
        i. Intended use doctrine
        ii. Lack of adequate directions for use
    d. Statements of identity, source, ingredients, or quality
    e. Danger to health when used according to labeling

C. Enforcement Tools and Procedures

1. Warning Letters (WLs) and Untitled Letters
    a. Recent areas of focus
2. Use of Media/Publicity
3. License Suspension and Revocation
4. Recalls
5. Seizure
6. Suits for Injunctions
    a. Preliminary injunctions
    b. Permanent injunctions
7. Consent Decrees
    a. Permanent injunctions

b. Disgorgement
c. Continuous FDA oversight and operations

8. Civil Money Penalties
9. Criminal Fines
10. Criminal Prosecutions
    a. Strict liability without criminal intent
    b. Individual liability and the *Park* Doctrine
    c. Misdemeanors vs. felonies
    d. Penalties
11. Office of Criminal Investigations (OCI), Criminal Process Referrals, U.S. Department of Justice

D. International

1. Harmonization
2. "Cluster" Meetings
3. Project Orbis

E. Imports

1. Importation from foreign sources
2. Import for export
3. Role of U.S. Department of Homeland Security (DHS) / Customs and Border Protection (CBP) Import Detentions and Refusals
4. Importation for Emergency Use

F. Exports

1. Exporting Unapproved Biologicals and Vaccines

5:00 PM	**Adjournment**

FDLI would like to thank Catherine M. Cook, Principal for Regulatory Policy, Greenleaf Health, Inc. for serving as our Curriculum Advisor for this course and for his assistance and support of FDLI's Educational Programs.