Introduction to Biologics and Biosimilars Law and Regulation

March 9-11, 2021 | Virtual Event

Tuesday, March 9

12:00 PM  FDLI Welcome and Announcements
Khara L. Minter, Assistant Director, Training Programs, FDLI

12:05–1:15 PM  I. Overview of Biological Products and FDA’s Regulatory Processes

Learning Objectives

- Learn the current regulatory framework and major statutory underpinnings of how key federal and state agencies regulate biological products
- 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 define biological products

Nathan A. Beaver, Partner, Foley & Lardner LLP

A. Landmark Legislative Enactments for Biologics Regulation and Development of Today’s Statutory Framework for Biologics
   1. The 1902 Biologics Act
   2. Federal Food, Drug, and Cosmetic Act of 1938 (FDCA)
   3. Public Health Service Act of 1944 (PHSA)
   4. The Food and Drug Administration Modernization Act of 1997 (FDAMA)
   5. Food and Drug Administration Amendments Act of 2007 (FDAAA)
   6. Biologics Price Competition and Innovation Act (BPCIA)
   7. Food and Drug Administration Safety and Innovation Act (FDASIA)
   8. Prescription Drug User Fee Act and Biosimilars User Fee Act (and reauthorizations)
   9. 21st Century Cures Act

B. Food and Drug Administration
   1. History
   2. FDA Mission
   3. Responsibilities and Structure of Headquarters and the Field
   4. Relative roles of CBER and CDER (historically and today)
      a. Concepts of “drug” and “biological product”
      b. Therapeutic proteins versus other biological products (e.g., vaccines)

C. FDA’s Place in Government and Additional Relevant Entities
   1. HHS in Federal Government
   2. FDA within HHS
3. Distinct missions but potentially overlapping roles of HHS agencies for biologics
   a. Center for Medicare and Medicaid Services (CMS)
   b. HHS Office of Inspector General (OIG)
   c. National Institutes of Health (NIH)
   d. Centers for Disease Control and Prevention (CDC)
   e. Animal and Plant Inspection Service (APHIS)

D. Sources of Legal and Regulatory Requirements and FDA Policies
   1. Statutes: FDCA and PHSA (structure/sections)
   2. Regulations
      a. Federal Register Notices
   3. Guidance Documents/CPGs
      a. Advisory opinions and Preambles
      b. Good Guidance Practices (GG)
      c. Staff manuals, guides and programs
   4. Enforcement actions and letters
      a. Citizen Petition responses
      b. Informal statements and advice

E. Standards
   1. International Conference on Harmonization (ICH)
   2. United States Pharmacopeia (USP)

F. Participating in FDA Policy Making
   1. Lobbying Congress
   2. PDUFA and BsUFA negotiations
   3. Comments on proposed regulations and draft guidance
   4. Participation in public meetings
   5. Citizen Petitions (FDA and HHS options)
   6. Judicial review

G. Product Specific Regulatory Proceedings
   1. Informal adjudications
      c. Dispute resolution, appeals
      d. Office of Chief Mediator and Ombudsman
   2. Regulatory hearings
   3. Formal adjudications
   4. Judicial review

H. Obtaining and Protecting Information under the Freedom of Information Act (FOIA)
   1. Mandatory Disclosures on Request
      a. Categories of disclosable information
      b. Nine Exemptions from mandatory disclosure
         i. Focus on trade secrets/commercial/financial information that is confidential or privileged
         ii. Disclosure prohibited by another federal law
         iii. Privileged communication between agencies
   2. Discretionary disclosure on request
   3. Preventing disclosure of information submitted to FDA
      a. Pre-submission review by FDA
b. Right to notice of proposed disclosure

c. Reverse FOIA litigation

1:15–1:25 PM  
Break

1:25–2:40 PM  
III. 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
- Examine market exclusivities and intellectual property

**Kellie B. Combs**, Partner, Ropes & Gray LLP

A. Basic Principles

1. Definitions drive jurisdiction and pathway
2. The key principle: Intended use
3. Statutory definitions
   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
4. Transition of Certain Drugs to Biologics Status
   a. Scope
   b. Transition provisions
      i. Pathway(s) to market
      ii. Patent litigation and exclusivity
      iii. Status after 2020

B. Pathways to Market – How to Determine Which Pathway to Choose

1. Biologics License Application (BLA)
   a. Full BLA
   b. Abbreviated BLA (biosimilar 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

C. Combination Products

1. General Rules
   a. Product jurisdiction and classification
   b. Primary Mode of Action (PMOA)
2. Procedural Considerations  
   a. Office of Combination Products  
   b. Requests for Designation  
3. CDER, CBER, and CDRH Intercenter Agreements  

D. General Principles of Premarket Approval (Drug/Biologic)  
1. General sequence (preclinical, clinical, marketing application)  
2. Safe, pure, potent / substantial evidence of effectiveness  
3. Balancing risk and benefit  
4. Fast track and accelerated approval for serious or life-threatening illness  
5. Breakthrough therapies  

E. Market Exclusivities and Intellectual Property  
1. Regulatory Exclusivity  
   a. Reference product exclusivity  
   b. Orphan exclusivity  
   c. Pediatric exclusivity  
2. Patent Exclusivity  
3. Trade Secrets – Information shared with agency in support of application can be protected from public disclosure as commercially sensitive proprietary information  

2:40–2:50 PM Break  
2:50–3:50 PM IV. Regulation of Biological/Drug 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  
• Lean how to prepare for FDA interactions  
• Understand compliance and enforcement considerations  

Michael K. Stern, Of Counsel, Covington & Burling 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 Trial Process  
   a. Phase I, II, III  
   b. Exploratory INDs  
   c. Endpoints & Accelerated Approval  
   d. Phase IV
4. Human Subject Protection
   a. Informed Consent
   b. Institutional Review Boards (IRBs)

C. Obligations of Sponsors and Investigators
   1. Monitoring
   2. Safety Reporting
   3. Protocol Amendments
   4. Disqualification of Investigators
   5. Financial Disclosures

D. Clinical Trial Registration

E. Interactions with FDA
   1. Special protocol assessments
   2. Meetings (e.g., EOP2)
   3. Orphan drug status
   4. Breakthrough therapy designation
   5. Fast track status
   6. Regenerative Medicine/Advanced Therapy designation

F. 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

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

3:50–4:00 PM  Break

4:00–5:00 PM  V. Regenerative Medicine and Advanced Therapies (RMATs)

Learning Objectives

- Distinguish between human cellular and tissue-based products (HCT/P)
- Determine the regulatory framework for regenerative medicine products and discuss key definitions and eligible therapies
- Examine expedited programs for RMATs
- Recall emerging issues in gene editing, in-office procedures and stem cell manufacturing practices

Emily Marden, Counsel, Sidley Austin LLP
A. Expedited Programs for RMATs
   1. RMAT Designation vs. Fast Track, Breakthrough, Priority Review, and Accelerated Approval
   2. SOPP 8214: CBER’s INTERACT Program\TRIP
   3. Benefits and drawbacks of RMAT designation

B. HCT/P’s – Human Cellular and Tissue Based Products
   1. Regulated under Section 361 of PHS Act
   2. Regulated under Section 351 of PHS Act

C. Emerging Issues
   1. Gene editing
   2. In-office procedures (Stem Cell Procedures, Microbiota Transplantation)
   3. Stem cell manufacturing practices
   4. Coronavirus Treatment Accelerated Program (CTAP)
VI. Biologics License Applications (BLA)

Learning Objectives

- Assess historical and current standards of approval
- Summarize what standard FDA uses to approve a BLA submitted under section 351(a) of the Public Health Service Act (PHSA)
- Outline what is in a section 351(a) BLA
- Understand FDA’s review and decision processes

Christina M. Markus, Partner, King & Spalding LLP

A. Approval Standard
   1. Safe, pure, and potent
      a. FDA: Potency includes evidence of effectiveness
      b. Substantial Evidence (SE)

B. Content and Organization
   1. Safety and effectiveness data
   2. Manufacturing facilities, processes, and controls
   3. Packaging
   4. Proposed labelling
   5. Biological and Drug Master Files (BMFs, DMFs)
   6. Debarment Certification
   7. Clinical Trial Databank Compliance Certification
   8. Use of Common Technical Document

C. FDA Review
   1. User Fees
      a. Performance goals
      b. Review clock
   2. Interacting with FDA
      a. Meetings and communications under PDUFA
      b. Dispute resolution
   3. Advisory Committees
   4. Pre-Approval Inspections (PAIs)

D. FDA’s Decision
   1. Complete response and approval letters
      a. Responses to FDA adverse decisions
   2. Post-market Commitments
      a. Post-market studies and clinical trials
      b. Risk Evaluation and Mitigation Strategies (REMS)
   3. Clinical trial results posting
E. Other Approaches (CBER BLAs)
   1. Vaccines
   2. Blood and blood products
   3. Cellular and gene therapy products
   4. Xenotransplantation

1:15–1:25 PM Break

1:25–2:40 PM VII. 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

Krista Hessler Carver, Partner, Covington & Burling LLP

A. Definitions
   1. Reference product
   2. Biosimilar biologics
   3. Interchangeable biosimilar biologics

B. Biosimilar Pathway to Market
   1. Definition – Approval Standard
   2. General approach to pathway
      a. Stepwise
      b. Totality of evidence
   3. Application contents, including the latest thinking on:
      a. Extrapolation
      b. Immunogenicity
      c. Foreign comparator products

C. Interacting with FDA
   1. Biosimilar Product Development program meetings
   2. User fees

D. Scope of Approval
   1. Conditions of use
   2. Labeling and naming
   3. Post-market labeling changes
   4. Pharmacovigilance
   5. REMS
   6. Pediatric assessments
   7. Exclusivity
E. Interchangeable Biological Products
   1. Definition
   2. Relationship between FDA and state laws
   3. Interchangeable product exclusivity

F. Timing Issues
   1. Submission under 351(k)
   2. Approval under 351(k)
      a. Overview of framework
      b. Notice of commercial marketing
      c. Use of post-grant and inter partes review

2:40–2:55 PM Break

2:55–4:05 PM VIII. 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
   2. FDA Adverse Event Reporting (FAERS)
   3. Vaccine Adverse Event Reporting (VAERS)
   4. Office of Surveillance and Epidemiology
   5. Sentinel Initiative

B. Risk Assessment and Risk Management
   1. New safety information
   2. FDA’s authority to require post-market studies or trials
   3. FDA’s authority to impose a REMS
   4. Overview of REMS authorities
   5. Post-market studies and trials
   6. Withdrawal of approval

C. Post-Approval Changes
   1. Annual reports
   2. Changes–being–effected supplements
   3. Prior approval supplements

4:05–4:20 PM Break
Learning Objectives

Discuss emerging issues regarding the definition of “protein” (Teva lawsuit), the definition of “strength” for purposes of the BPCIA (Boehringer Ingelheim Citizen Petition), labeling carve-outs and special risks for biosimilars and interchangeable biological products (GlaxoSmithKline LLC v. Teva Pharm. USA, Inc., 976 F.3d 1347 (Fed. Cir. 2020)), unbranded biologics, Purple Book reforms, and FDA’s umbrella policy for Reference Product (RP) exclusivity.

Scott M. Lassman, Principal, Lassman Law + Policy
Thursday, March 11

12:00 PM  
FDLI Welcome and Announcements  
Khara L. Minter, Assistant Director, Training Programs, FDLI

12:05–1:20 PM  
X. Regulation of Biological Manufacturing

Learning Objectives

- Examine guidelines for establishment registration and listing
- Recall standards for inspections, recognize when a product is considered adulterated, and summarize current Good Manufacturing practices (cGMPs)
- Determine the scope of pre-license and pre-approval inspections (PAIs)
- Recognize FDA’s inspection authority and its enforcement process

Scott Kaplan, Counsel, Hogan Lovells US LLP

A. Establishment Registration and Listing

B. Standards of Inspections
   1. Adulteration
      a. Current Good Manufacturing Practices (cGMPs)
      b. Departure from Compendial or Represented Standards
      c. Insanitary conditions

C. Scope of Pre-Approval Inspections (PAIs)
   1. Clinical data
   2. Manufacturing
   3. Packaging
   4. GMP compliance
   5. 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)
A. FDA Institutions and Enforcement Powers
   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

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

F. Enforcement
   1. Untitled letters
   2. Warning letters (WLs)
      b. Recall of violative promotional labeling

G. Other Relevant Laws and Considerations
   1. Sunshine Act
   2. Fraud and Abuse / Anti-Kickback Statute
   3. False Claims Act

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 & Emory

A. Interstate Commerce Element

B. Prohibited Acts

C. Enforcement Tools and Procedures
   1. Warning Letters (WLs) and Untitled Letters
   2. Use of Media/Publicity
   3. Recalls
   4. Seizure
   5. Suits for Injunctions
      a. Preliminary injunctions
      b. Permanent injunctions
   6. Consent Decrees
      a. Permanent injunctions
      b. Disgorgement
      c. Continuous FDA oversight and operations
   7. Civil Money Penalties
   8. Criminal Fines
9. Criminal Prosecutions
   a. Strict liability without criminal intent
   b. Individual liability and the Park Doctrine
   c. Misdemeanors vs. felonies
   d. Penalties

D. International Harmonization

E. Imports
   1. Importation from foreign sources
   2. Import for export
   4. Importation for Emergency Use

F. Exports
   1. Exporting Unapproved Biologicals and Vaccines

4:30 PM Adjournment

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