Introduction to Drug Law and Regulation

November 9-10, 2021

Preconference Primer **I. Origins and Overview of the Food and Drug Administration (FDA) and the Regulation of Drugs**

Learning Objectives

- Learn the current regulatory framework and major statutory underpinnings for drug regulation
- Recognize the sources of legal and regulatory requirements and FDA policies
- Understand participation in FDA policy making

Nathan Beaton, Associate, Latham & Watkins LLP
Meryl E. Bartlett, Associate, Latham & Watkins LLP

A. Landmark Legislative Enactments for Drug Regulation and Development of Today's Statutory Framework

1. Historical Context/FDA's Place in Government
   a. HHS Oversight
2. Major Statutory Underpinnings
   a. Federal Food, Drug, and Cosmetic Act (FDCA) of 1938
   b. The Durham-Humphrey Amendment of 1951
   c. The 1962 Drug Amendments/Kefauver-Harris Act
      i. DESI Review
      ii. OTC Drug Review
   d. Drug Price Competition and Patent Term Restoration Act of 1984
   e. Prescription Drug Marketing Act of 1987
   f. Various User Fee Acts
3. Modern Statutory Underpinnings
   a. FDA Safety and Innovation Act (2012)
      i. Section 907: Inclusion of Demographic Subgroups in Clinical Trials
   b. Drug Quality and Security Act (2013)
   c. 21st Century Cures Act (2016)
   d. FDA Reauthorization Act (2017)
   e. The CARES Act (2020)

B. FDA Organization

1. President Biden Appointments

C. Sources of Legal and Regulatory Requirements and FDA Policies

1. Statutes: FDCA and Public Health Service Act (PHSA) of 1944
   a. Structure/Sections

2. Regulations
    a. Substantive Rules
    b. Interpretive Rules and Statements of Policy
3. Federal Register (FR) Notices
4. Advisory Opinions and Preambles; Advisory Committees
5. Guidance Documents; Good Guidance Practices (GGP)
6. Compliance Policy Guides (CPGs)
7. Staff manuals, guides, and programs
8. Enforcement actions and letters
9. Citizen Petition responses
10. Informal statements and advice
11. FDA's website
12. FDA Webinars
13. Obtaining and protecting information under the Freedom of Information Act (FOIA)

D. Participating in FDA Policymaking

1. Citizen Petitions
2. Rule-making comments and hearings
3. Comments on guidance documents
4. Public hearings and public meetings
5. Judicial Review

E. Product Specific Regulatory Proceedings

1. Informal Adjudications
    a. Dispute Resolution; Appeals
    b. Center and Agency Ombudsman
2. Regulatory Hearings
3. Formal Adjudications
4. Judicial Review

Preconference Primer II. The New Drug Approval Process: Basic Concepts

Learning Objectives

- Recognize the difference between a "drug" and a "new drug" under the Federal Food Drug and Cosmetic Act (FDCA)
- Learn the various approval pathways for bringing a new drug to the U.S. market
- Understand the scientific standards by which FDA will approve a new drug

Alexandre Gapihan, Associate, Morgan, Lewis & Bockius LLP

A. What is a Drug?

1. Statutory and Regulatory Definitions
2. The key principle: Intended use
3. Drugs vs. Other FDA Regulated Products
    a. Drug vs. Food
    b. Drug vs. Dietary Supplement
    c. Drug vs. Medical Device
    d. Drug vs. Cosmetic

e. Drug vs. Combination Product
f. Biologics
g. Animal Drugs
h. Tobacco

B. What is a New Drug?

1. Exception for drugs that are generally recognized as safe and effective
2. Exception for drugs that are subject to 1938 and 1962 grandfather clauses

C. Legal Standard for Approval of New Drugs

1. Effectiveness – Substantial Evidence (SE)
2. Adequate and Well Controlled Studies
3. Safety – Balancing Risk and Initial Benefit
    a. Determination of safety and risk
    b. Differing perspectives on safety (pre-approval and post-approval analyses)

D. New Drug Approval Pathways

1. New Drug Application (NDA)
2. Abbreviated New Drug Application (ANDAs)
3. Section 505(b)(2) Application
4. Animal Rule
5. Limited Population for Antibacterial and Antifungal Drugs
6. Emergency Use Authorization

Tuesday, November 9

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

11:05 AM–12:15 PM **III. The New Drug Approval Process: New Drug Research and Development**

Learning Objectives

- Learn the requirements of Good Laboratory Practices (GLP) and Good Clinical Practices (GCP)
- Understand the fast-track review process
- Learn the requirements for pediatric testing and orphan drugs

Marc Wagner, Associate, BakerHostetler

A. Preclinical Testing/Investigation

1. "Good Laboratory Practice" (GLP) Regulations
2. Preclinical Data Requirements

B. Clinical Testing/Investigation and Good Clinical Practice (GCP) Requirements

1. Investigational New Drug (IND) Applications

2. Phase I, Phase II, Phase III
    a. Recruitment and enrollment of underrepresented sexes, race/ethnicity minority groups
    b. Clinical trial design, diversifying clinical trials
3. Meetings with FDA
4. Role of the Protocol
5. Informed Consent
6. Institutional Review Boards (IRBs)
7. Obligations of Sponsors and Investigators; Role of Contract Research Organizations (CROs)
    a. Monitoring
    b. Adverse Event Reporting (AER)
    c. Financial Disclosures
8. Clinical Holds
9. Use of Foreign Studies
10. Exemptions from the IND Requirement
11. Disqualification of Investigators/Debarment

C. Pediatric Testing

1. Pediatric Research Equity Act of 2003 (PREA)
    a. Waivers and Deferrals
2. Pediatric Exclusivity

D. Expanded Access and Right to Try

E. Orphan Drugs

1. Orphan Drug Designation
2. Orphan Drug Exclusivity
    a. Clinical Superiority
3. FDA Assistance in Study Design

F. Clinical Trials Registry

1. ClinicalTrials.gov: statutory and regulatory requirements
2. Medical Publisher Policies

G. 21st Century Cures Act

1. Patient-focused drug development
2. Real world evidence
3. Novel clinical trial designs
4. Qualification of drug development tools

12:15–1:00 PM IV. FDA's COVID-19 Activities

Learning Objectives

- Learn about FDA's regulatory pathways for the approval and investigation of products intended for the prevention and treatment of COVID-19
- Understand actions that FDA has taken to assist industry during the COVID-19 pandemic
- Learn about FDA COVID-19 enforcement

Angela M. Seaton, Partner, Shook, Hardy & Bacon LLP

A. Primary Impacted Product Offerings

1. Vaccines – Center for Biologics EUAs
   a. Vaccine/drug access for minorities
2. Therapeutics, proteins – Center for Drugs EUAs and the Coronavirus Treatment Acceleration Program
3. Hand Sanitizer – OTC Monograph and Temporary Policies
4. Compounded Drugs – CDER Temporary Policies
5. Center for Devices: Diagnostic Tests for SARS-CoV-2 – Center for Devices
6. Personal Protective Equipment (PPE)
7. Ventilators

B. Exemptions, Exclusions and Pauses during the Public Health Emergency

1. Emergency Use Authorization vs. traditional approval
2. Clinical Trial requirements
   a. Renewed receptivity of real-world data/real-world evidence
3. Application Review Timelines and User Fee Meetings
4. Facility Inspections
5. Manufacturing Operations
6. DSCSA Supply Chain requirements
7. Risk Evaluation and Mitigation Strategy (REMS) requirements
8. Drug Sample Program requirements
9. Adverse Event Reporting
10. Not Exempt: Notifications of Permanent Discontinuance or Interruption in Manufacturing

C. Unprecedented Public Outreach

1. Temporary Policies to expand Industry Participation
2. Notice of Availability publishing guidances in groups
3. Daily COVID Updates
4. Consumer Updates and Toolkits
5. Enforcement Actions – False and Misleading Claims

1:00–1:15 PM **Break**

1:15–2:25 PM **V. The New Drug Approval Process: NDA Submission and Review**

Learning Objectives

- Recognize the content and organization of a full New Drug Application
- Become familiar with:
  - User fees and goals under the Prescription Drug User Fee Act (PDUFA)
  - Expedited review programs
  - Best practices when interacting with FDA

Elizabeth Mulkey, Senior Associate, Goodwin Procter LLP

A. Content and Organization of a Full NDA

1. Safety and Effectiveness Data
2. Chemistry, Manufacturing, and Controls (CMC) Information
3. Container/Closure and Packaging
4. Proposed Labeling
5. Patent Information
6. Drug Master Files (DMFs)
7. Certification and Disclosures
8. Proprietary Name
9. Use of the Common Technical Document

B. The Review Process

1. User Fees and Goals (PDUFA)
2. The Review Clock and the Impact of PDUFA
3. Interacting with FDA
    a. Good Review Management Principles (GRMP)
    b. Special Protocol Assessment (SPA)
    c. Meetings with FDA
    d. Advisory Committees
4. Pre-Approval Inspections (PAIs)
5. Complete Response and Approval Letters

C. Expedited Programs

1. Fast Track Designation
2. Priority Review
3. Accelerated Approval
4. Breakthrough Therapy Designation
5. For "unmet medical need" in treatment of a "serious condition"

D. Responses to FDA Adverse Decision

1. Right to a hearing on refusal to approve an application
2. Judicial review of refusal to approve an application
3. Judicial review of approval of a competitor's application
4. FDA and CDER Ombudsman/Dispute Resolution

E. Post-approval Study and Surveillance Requirements

1. Risk Evaluation and Mitigation Strategies (REMS)
2. Safety Labeling Changes
3. Postmarketing Study Requirements

F. Critical Path Innovation Meetings

2:25–3:35 PM **VI. The Abbreviated NDA (ANDA), 505(b)(2) Applications, and Patent and Exclusivity Issues**

Learning Objectives

- Understand the generic drug approval pathway and requirements of sameness, bioequivalence, and therapeutic equivalence
- Recognize patent listing and certification requirements and implications for Hatch-Waxman patent infringement cases and generic drug approval
- Learn eligibility requirements and scope of various market exclusivities for innovator and generic products

Rebecca L. Dandeker, Partner, Morgan, Lewis & Bockius, LLP

A. Eligibility for ANDA Consideration

1. Reference Listed Drug
2. Reference Standard
3. *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book)
4. Suitability Petitions

B. Content and Organization of an ANDA

C. Sameness, Bioequivalence, and Therapeutic Equivalence

D. Office of Generic Drugs' Review Process

1. GDUFA I (2012) – Program Goals
2. GDUFA II (FDA Reauthorization Act, 2017) -Program Goals and Fee Types
3. R&D Phase
    a. Pre-ANDA Meetings
    b. Controlled Correspondence
    c. Product-Specific Guidances
    d. Inactive Ingredient Database
    e. Self-Identification
4. Expedited Programs: Priority ANDAs, Competitive Generics
5. Responses to OGD Adverse Decisions
    a. Refuse to Receive
    b. Complete Response Letter
    c. Requests for Reconsideration
    d. Formal Dispute Resolution

E. 505(b)(2) Applications

F. Patent Provisions

1. Patent Listing
2. Patent Certifications
    a. Paragraph I, II, III, IV Certifications
    b. Notice of Paragraph IV Certification

c. Challenges to Patent Listings
3. 30-Month Stays on ANDA and 505(b)(2) Approvals
4. The Orange Book Modernization Act (signed Jan. 2021)

G. Market Exclusivity

1. For Innovator Products
   a. 5-Year Exclusivity for New Chemical Entities (NCEs)
   b. 3-Year Exclusivity based on New Clinical Investigations
   c. Pediatric Exclusivity, 6 months
   d. Orphan Drug and Antibiotic (GAIN) Exclusivities
2. For Generic Products
   a. 180-Day First Applicant Exclusivity
   b. 180-Day Competitive Generic Therapy Exclusivity

H. Strategies Affecting Approval

1. Challenges to eligibility for generic approval
2. Development of new conditions of use for RLDs
3. Authorized Generics
4. REMS: Access to Product Samples and Shared System REMS

3:35–3:50 PM **Break**

3:50–5:00 PM **VII. Post-Approval Issues**

Learning Objectives

- Understand regulatory requirements for post-approval safety reporting
- Explain FDA's drug safety activities
- Describe the regulatory framework for post approval changes and supplemental New Drug Applications (NDAs) and Abbreviated NDAs (ANDAs)
- Understand at a high-level:
  - Grounds for Withdrawal of Approval
  - Medicare, Medicaid and Reimbursement Issues
  - Drug Supple Chain Security Act (DSCSA) Product Tracing Requirements

Frederick A. Stearns, Partner, Keller and Heckman LLP

A. Adverse Drug Experience (ADE) Reports

B. Annual and Other Reports

1. Field Alert Reports
2. Notification of Permanent Discontinuance or Interruption in Manufacturing

C. FDA Drug Safety Activities

D. Post-Approval Changes and Supplemental NDAs (sNDAs) and ANDAs

E. Grounds for Withdrawal of Approval

F. Medicare, Medicaid and Reimbursement Issues

G. Drug Supply Chain Security Act (DSCSA) Product Tracing Requirements

Wednesday, November 10

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

11:05 AM–12:05 PM **VIII. Biologics and Biosimilars**

Learning Objectives

- Understand differences between biologics and small molecule drugs and effect on regulating generic drugs and biosimilars
- Learn regulatory standards for biosimilars and interchangeable biosimilars
- Discuss the regulatory exclusivities available for biologics
- Address the differences between switching and substitution
- Explore the Patent Dance

Christopher Gallo, Associate, Axinn, Veltrop & Harkrider LLP

A. What is a Biologic?

B. Drug vs. Biologic

C. Biologics License Application (BLA) Approval Standards

D. What is a Biosimilar?

E. Biosimilar Approval Standards

F. Interchangeable Approval Standards

G. Exclusivity (Biologic and Interchangeable)

H. Biosimilar Labeling

I. Nonproprietary Naming of Biologics

J. The "Deemed to be a License" Provision

K. Overview of Patent Scheme

L. State Substitution Laws

M. Advertising and Promotion

1. Draft Guidance, Promotional Labeling and Advertising Considerations for Prescription Biological Reference and Biological Products
2. Biosimilars Action Plan
3. FDA/FTC Collaboration to Advance Competition

N. The Purple Book Continuity Act (signed Jan. 2021)

12:05–1:05 PM IX. Regulation of Over-the-Counter (OTC) Drugs

Learning Objectives

- Learn how Over-the-Counter (OTC) drugs are regulated by the FDA
- Understand the history of the OTC Drug Review Process
- Explore how the Coronavirus Aid, Relief, and Economic Security (CARES) Act modernized the OTC Drug Review Process and the future of OTC Drugs

Deborah L. Livornese, Director, Hyman, Phelps & McNamara, PC

A. Rx vs. OTC Status

1. Statutory Definition

B. The OTC Review and the Monograph Process

1. Legal Nature and Basis
2. Scope of Review
3. Completing and Amending the Monograph
    a. Requirements pending monograph completion
    b. Updating the monographs
4. Monograph Requirements
    a. Ingredients
    b. Conditions for Use / Labeling Claims
5. Marketing New Dosage Forms under the OTC Review
6. New OTC Drug Labeling Requirements
7. Time and Extent Application (TEA)
8. The CARES Act of 2020 – OTC Monograph Reform
    a. Monograph Conversion to Administrative Orders
    b. Addressing Safety Issues and Facilitating Innovative Changes
    c. FDA-initiated changes via Administrative Order process
    d. OTC Monograph Order Requests (OMOR) – for industry-requested changes and additions to OTC Monograph conditions
    e. 18-month Exclusivity
    f. User Fees
        i. Annual Manufacturer Facility Fee
        ii. OMOR Fee

C. OTC by NDA

D. Rx-to-OTC Switches

1. By Monograph
2. By NDA
3. The Switch Regulation
4. Non-Patent Exclusivity
5. “Forced” OTC Switches
6. Partial OTC Switches, e.g. Plan B

E. “Behind-the-Counter” OTC Drugs

1:05–1:15 PM **Break**

1:15–2:15 PM **X. Regulation of Drug Manufacturing**

Learning Objectives

- Learn Current Good Manufacturing Practices (cGMPs) for drugs and be able to define "adulteration" and "misbranding"
- Understand the different types of inspections, including the differences between foreign and domestic inspections
- Recognize the elements of a 483 observation and the components involved in closing out an inspection

Peter V. Lindsay, Partner, Paul Hastings

A. Establishment Registration and Drug Listing

B. Adulteration

1. Departure from Compendial or Represented Standards
2. Insanitary Conditions
3. Supplier Quality

C. Misbranding

D. Inspections (Foreign and Domestic)

1. Inspection Process and Procedure
2. Search Warrants
    a. Administrative
    b. Criminal
3. Photographs and Recordings
4. Affidavits and Declaration
5. Types of Inspections
    a. Routine
    b. For Cause
    c. Follow Up
    d. Pre-Approval Inspection (PAI)
6. COVID-19: Suspension of On-site Inspections; then Prioritization, Pre-announced and Remote Inspections

E. Current Good Manufacturing Practice (cGMP)

1. Adulteration GMPs

F. Responding to 483 Observations – Closing an Inspection

1. Establishment Inspection Report (EIR)
2. Import Alerts
3. Supply Chain Issues

2:15–2:30 PM **Break**

2:30–3:30 PM XI. Regulation of Drug Marketing

Learning Objectives

- Learn to differentiate between "label" and "labeling" and "false and "misleading"
- Gain insight on FDA's social media guidance, use of off-label information, and considerations for other government and state entities
- Understand the role of a corporate compliance program in managing the risks of marketing a drug

Heather Banuelos, Counsel, King & Spalding LLP
Gillian M. Russell, Counsel, King & Spalding LLP

A. Key Principles of Advertising and Promotion

1. Basic definition and concepts of labels, labeling and advertising
2. Intended Use and the New Drug Approval Requirement
3. Misbranding
    a. Adequate Directions for Use
    b. False or Misleading Labeling
    c. Material Omissions
    d. Lack of Adequate Directions or Warning
4. Office of Prescription Drug Promotion (OPDP)
    a. Preclearance
    b. Submission Requirements
    c. Post Marketing Letters
    d. Corrective Actions

B. Prescription Drug Promotion

1. Promotional Labeling vs. Advertisements
2. Conformance with Approved Labeling
3. Fair Balance
4. Brief Summary for Advertisements
5. Comparative Claims
6. Pharmacoeconomic/healthcare economic/outcomes information
7. Patient Reported Outcomes
8. Interactions with SEC
9. Use of Internet, Electronic and Social Networking Media

C. Off-Label Information and Other Current Issues

1. First Amendment Issues Relating to the Dissemination of Information on Off-Label Uses
2. Disease and Help Seeking Ads
3. Pre-approval Promotion and Advertising
4. Scientific and Educational Activities
5. Use of Medical Science Liaisons (MSLs); Unsolicited Requests for Information by Medical Professionals
6. Good Reprint Practices
7. Communications with payors, formulary committees, and similar entities

8. Consistent with FDA-approved Labeling (CFL)

D. OTC Drugs
1. Labeling – Regulated by FDA
2. Advertising – Regulated by FTC
3. National Advertising Division (NAD)

E. Anti-Kickback Statute and Open-Payments Reporting Rules

F. False Claims Act

G. Other Considerations – the States, Product Liability, the Lanham Act; PhRMA Code, Price-Reporting and Pricing Transparency

H. Medicare/Medicaid Fraud

I. Corporate Compliance Programs
1. Codes of Conduct
2. Corporate Integrity Agreements (CIAs)

3:30–3:45 PM **Break**

3:45–5:00 PM **XII. Violations and Enforcement**

Learning Objectives

- Understand the sources and scope of FDA's enforcement authorities
- Explore FDA's administrative enforcement tools (including inspections, 483s, and Warning Letters) and the circumstances in which FDA uses them
- Highlight and examine FDA's authority to seek civil injunctions, seize violative products from the market, and conduct criminal investigations into problematic activity

Tiffany Humphries, Senior Associate, Baker McKenzie

A. The Interstate Commerce Element

B. Prohibited Acts

C. Enforcement Tools and Procedures
1. Warning Letters (WLs) and Untitled Letters
2. Use of Media/Publicity
3. "Voluntary" Recalls
4. Civil Penalties/Disgorgement
5. Seizure Actions
6. Suits for Injunctions, Consent Decrees
    a. Preliminary Injunctions before Trial
    b. Permanent Injunctions and Consent Decrees
    c. Continuous FDA Oversight of Operations
7. Criminal Prosecutions
    a. Strict Liability without Criminal Intent

b. Individual Liability and the *Park* Doctrine
c. Misdemeanors vs. Felonies
d. Penalties
e. Office of Criminal Investigations (OCI), Criminal Process Referrals, U.S. Department of Justice (DOJ)

8. How FDA Decides an Enforcement Action
    a. What motivates FDA to take action, e.g. not sending two warning letters on the same type of violation
    b. Enforcement action against a competitor
9. Debarment
10. Application Integrity Policy (AIP)
11. Imports Detention/Refusals and Alerts

D. FDA Commissioner's Enforcement Initiatives

1. Unapproved and Counterfeit Drug Initiatives
2. Other Policies
    a. Post-Inspection Deadlines
    b. Shift in OCC Review
    c. Development of Risk Control and Enforcement Strategies with Regulatory Partners
    d. Increased Commitment to Warning Letter and Recall Follow-Up
    e. Swift, Aggressive, Immediate Enforcement Action When Indicated
    f. Warning Letter Close-Out Process
    g. Addressing the Opioid Abuse Crisis
    h. Improving the Quality of Compounded Drugs
3. Current Enforcement Priorities

5:00 PM	**Adjournment**

FDLI would like to Rebecca L. Dandeker, Partner, Morgan, Lewis & Bockius LLP, for serving as our Curriculum Advisor for this course and for her assistance and support of FDLI's Educational Programs.