ARNOLD & PORTER LLP

Regulatory Affairs Professionals Society:
Regulatory Affairs Certification (RAC) Study Group

Overview of the FDA: History, Regulatory Framework, and the APA

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Agenda

- FDA History
- Overview of FDA Responsibilities
  - Generally
  - Drugs, Biologics, and Devices
- FDA Regulation – Basic Principles
- FDA Regulatory Framework
- Administrative Procedure Act (APA)

FDA History

Food and Drug Administration (FDA) – History

- 1848: Import Drugs Act
  - Passed after American troops in Mexico suffer when given counterfeit malaria medicine
  - Chemical analysis of agricultural products in the Patent Office
- 1862: Department of Agriculture took over the chemical analysis function
- 1902: Biologics Control Act
  - Passed after 13 children die in 1901 as a result of tetanus-infected diphtheria antitoxin
- 1906: Modern regulatory functions begin with the Food and Drug Act
  - Prohibited adulterated and misbranded food and drugs in interstate commerce
- 1938: Food, Drug, and Cosmetic Act (FDCA)
  - Passed after more than 100 people die in 15 states in 1937 as a result of an elixir that was mixed with antifreeze and administered to treat strep infections.
  - Provisions
    - Requires new drugs to be shown safe before marketing
    - Removes need to show intent to defraud in drug misbranding cases
    - Authority to police medical devices
    - Adds remedy of court injunctions

FDA History

- 1962: Drug amendments to FDCA
  - Passed after US avoided tragedy when FDA refuses to allow thalidomide on the market
    - Drug resulted in birth of thousands of malformed babies in Europe
  - New amendments tightened control over drugs and required information about adverse effects
- 1976: Medical Device Amendments authorize FDA to pre-approve medical devices
  - Passed after widespread pacemaker failures and injuries from intrauterine devices are reported
- 1983: FDA issues Tamper-Resistant Packaging requirements and Federal Anti-Tampering Act
  - Passed after 7 people die from Tylenol laced with cyanide
- 1988: Food and Drug Administration Act
  - FDA officially established as agency of Department of Health and Human Services.
- 1990: Safe Medical Devices Act
  - Passed after reports of injuries and deaths in nursing homes due to faulty medical devices and injuries from permanently implanted devices, such as breast, implants begin to surface
  - Provides greater control over medical devices including power to recall devices and requiring post-market research.

Overview of FDA Responsibilities

FDA Responsibilities

- Foods (except meat from livestock, poultry, and some egg products)
- Human and veterinary drugs
- Vaccines and other biological products
- Medical devices
- Electronic product radiations
- Cosmetics and dietary supplements
- Tobacco products

FDA Drug, Biologic, and Device Regulation

- Prescription and Non-Prescription Drugs
  Center for Drug Evaluation and Research (CDER)
  - Safety, effectiveness, and quality
  - Labeling
  - Manufacturing standards

- Vaccines and other Biologics
  Center for Biologics Evaluation and Research (CBER)/
  Center for Drug Evaluation and Research (CDER)
  - Product and manufacturer licensing
  - Safety of the blood supply
  - Establish product standards

- Medical Devices
  Center for Devices and Radiological Health (CDRH)
  - Registration and Listing, 510(k) Premarket Clearance ,Premarket Approval (PMA)
  - Manufacturing and performance standards
  - Tracking performance and adverse events

- Level of regulatory oversight dependant on categorization of product

Categorizing Drugs

- Over the Counter (OTC): A prescription is not required when FDA finds:
  - "such requirements are not necessary for the protection of the public health."

  and
  - "the drug is safe and effective for use in self-medication as directed in proposed labeling."

- Prescription (Rx): A prescription is required if a drug:
  - "is not safe for use except under the supervision of a practitioner licensed by law to administer such drug.

  or
  - "is limited by an approved application…to use under the professional supervision of a practitioner licensed by law to administer such drug."

Bringing a Drug to Market

- Investigational New Drug Application
  - Information about proposed clinical studies
  - Must be filed before clinical studies begin
- Clinical Trials
  - Four phases to gather information about the drug's efficacy and effectiveness
- New Drug Application (NDA)
  - Contains information about clinical trial results, manufacturing process, and product description
  - FDA evaluates drug's safety and effectiveness data, analyzes samples and inspects facilities, and checks labeling for accuracy
- Approval: Once approved FDA oversight continues through post-market regulatory procedures (Phase IV)
- Generic drugs: Abbreviated New Drug Application (ANDA)
  - Generally not required to include preclinical and clinical data
  - Need to show bioequivalence

Bringing a Biologic to Market

- In contrast to chemically synthesized small molecular weight drugs, which have a well-defined structure and can be thoroughly characterized, biological products are generally derived from living material – human, animal, or microorganism – are complex in structure, and thus are usually not fully characterized.

- Biologics include blood-derived products, vaccines, in vivo diagnostic allergenic products, immunoglobulin products, products containing cells or microorganisms, and most protein products.

- FDA has concurrent authority under the FDCA and PHS to regulate Biologics
  - Investigational New Drug Application
  - Biologic License Application

- The Affordable Care Act created a biosimilar pathway, which is analogous to abbreviated approval for generic drugs.
  - A biosimilar must be “highly similar” regarding safety, purity, and potency and “interchangeable” with the reference biologic.

- Once approved the FDA continues to regulate post-market activities

Defining Medical Devices

- A medical device is an "instrument, apparatus, implement, machine, contrivance . . . or other similar or related article, including any component, part, or accessory"
  - intended for use in the *diagnosis, treatment, cure*, or prevention of a *disease or condition*, or
  - intended to affect the *structure or function* of the body
  - which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is *not dependent upon being metabolized* for the achievement of its primary intended purposes
    - *See* 21 U.S.C. § 321(h)

Classifying Devices

- Premarket requirements driven by Classification of device
  - Class I: Low risk and typically exempt from premarket authorization (e.g., massagers, toothbrushes, surgical gloves)
    - Registration and Listing
  - Class II: Intermediate risk (e.g., hospital sterilizers, diagnostic software)
    - 510(k) clearance through a finding of substantial equivalence to a predicate device
  - Class III: High risk (e.g., pace maker, heart valve)
    - Premarket Approval (PMA)

- Over 1800 medical device types are classified by regulation
  - If device matches the regulations, then the regulation controls
  - If device does not match any regulation, then the manufacturer may:
    - Use its best judgment about what, if any, authorization is required
    - Ask FDA for a non-binding device determination
  - Getting this wrong can result in FDA enforcement actions or delays to market

- Post-market requirements – "general controls" which include:
  - Registration and Listing
  - Good Manufacturing Practice (GMP)/Quality System Regulation (QSR) requirements
  - Adverse Event reporting through Medical Device Reports (MDRs)

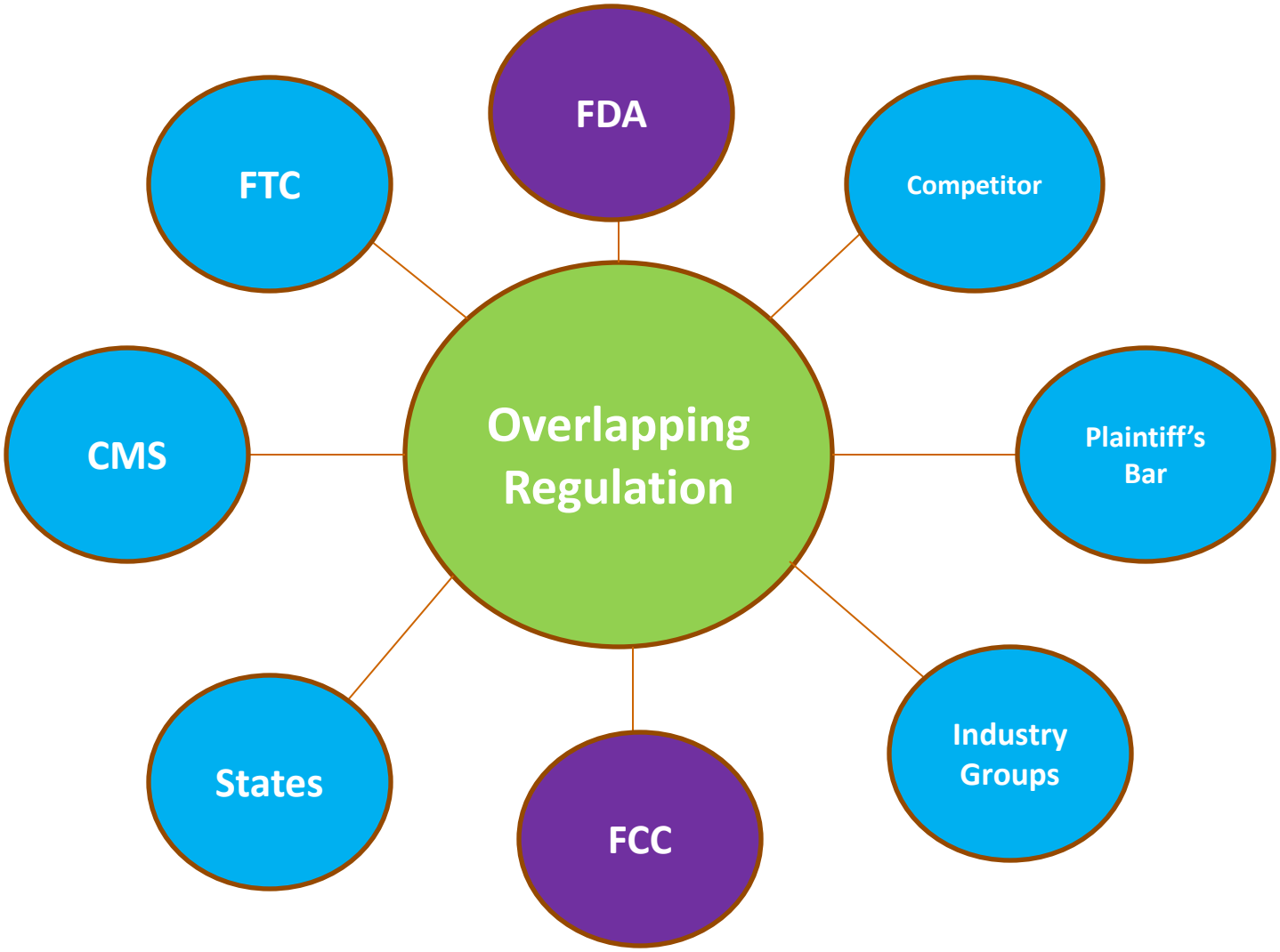
FDA Regulation – Basic Principles

Basic Principles of FDA Regulation – Broad Authority

- The Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to regulate a variety of health-related products
- Regulation of all aspects of product development and sale
  - Design and composition
  - Manufacture and approval
  - Marketing
- Two-Pronged Approach
  - Issue regulations
  - Review actions

Basic Principles of FDA Regulation – Broad Authority

- Products cannot be marketed without appropriate premarket approval unless they are exempt from such requirements
- Products must be designed and manufactured to ensure safety and efficacy
- Manufacturers, importers, distributors, and certain product users ("user facilities") must collect, evaluate and report adverse events to FDA, although requirements differ slightly for each group
- Every entity and individual in the product marketing or supply chain has potential liability for statutory violations if they distribute or further the distribution of non-compliant products


FDA
FTC
Competitor
CMS
Overlapping Regulation
Plaintiff's Bar
States
FCC
Industry Groups

Types of Entities Regulated by FDA

- U.S. and foreign "**owners and operators**" of companies or facilities that make, distribute, or market FDA-regulated products
- "**Responsible corporate officers**" who manage or oversee those companies or facilities
- "**Applicants**" or "**sponsors**" who conduct or oversee **clinical trials** (*i.e.*, research on humans) or submit research or marketing applications to FDA

FDA Regulatory Framework

FDA Regulatory Framework

- FDA issues regulations and guidance on content and format, including:
  - Statements on product uses and prescribing information
  - Brief summary relating to side effects, contraindications, and effectiveness (statement of Important Safety Information (ISI))
  - Instructions for use
  - Prominence of statements; clarity of messages
- FDA reviews product labeling, advertising, and promotional activity
  - Must not be **"false or misleading** in any particular**"**
  - FDA considers not only words or statements, but also designs and images, format and placement of text
  - Claims must be within the scope of approved labeling or within scope of marketing authorization or classification regulation – focus on **safety and efficacy** claims
  - Risks and benefits must be presented in a fair/balanced manner
  - Must contain material facts regarding consequences that may result from the use of the product under normal conditions

Intended Use

- The FDCA defines most FDA-regulated products based on their intended use
  - See 21 U.S.C. § 321 (defining drug, device, cosmetic, etc. based on intended use)
- Intended use refers to the "objective intent" of the persons legally responsible for marketing the product, and is shown by:
  - Labeling (e.g., packaging, user manuals, medication guides, other information that is integral to a transaction or necessary to ensure safe use of the product
  - Promotional Statements (e.g., advertising, sponsorships, or other activities intended to raise awareness of a business or product, or surrounding content/graphics are important factors)
  - Other Statements Made By or On Behalf Of the Marketer (e.g., securities registration, patent filings, testimonials, oral statements by sales reps, depictions of conduct or use)
- Actual Knowledge of the marketer as to end user intent; circumstances of marketing
  - See 21 C.F.R. § 801.4

Prohibited Acts

- The FDCA lists over 30 "prohibited acts"
  - No specific intent to violate the law is required
  - Liability attaches based on evidence that a violation has occurred (i.e., strict liability)

- Committing prohibited acts or "causing" such acts to be committed violates the FDCA
  - "Causing" is not defined in the statute; FDA has broad discretion to define
  - "Causing" can include aiding and abetting, inducement of illegal activity, willful ignorance of illegal acts

- FDCA "prohibited acts" can be criminal violations under other statutes (*e.g.*, mail and wire fraud, false statements, conspiracy, etc.)

Adulterated or Misbranded Products

- The FDCA prohibits distribution of adulterated or misbranded products in interstate commerce
- Many actions can cause a product to become adulterated or misbranded, for example:
- Product may become adulterated if . . .
  - It is contaminated
  - It is made or held in insanitary conditions or manufactured in violation of quality system regulation (QSR) (e.g., management oversight, employee training, documentation, SOPs for design, production, and process controls, CAPA, and MDR)
  - Its packaging is poisonous or harmful to health
  - It is marketed for an unapproved use
- Product may become misbranded if . . .
  - Its marketing is false or misleading
  - Its packaging lacks required information, disclosures and warnings
  - Is manufactured in a facility that is not appropriately registered with FDA

FDA Enforcement Actions

- Inspections
  - The FDCA authorizes FDA to inspect registered medical device establishments
- Criminal sanctions (corporations and individuals)
  - *United States v. Park*, 421 U.S. 658 (1975) – "Responsible corporate officers" can be held vicariously liable for unlawful acts of corporation or agents
- Civil sanctions (corporations and individuals)
  - Civil money penalties
  - Seizures and injunctions
- FDA may use administrative authority
  - Untitled Letters
  - Warning letters
  - Adverse publicity
  - Import alerts/detentions
  - Recalls

FDA Enforcement Actions

- Active surveillance and monitoring:
  - Media surveillance (e.g., newspapers, journals, television, radio, internet, and social media)
  - Meetings and Trade Shows (e.g., attends medical conventions and visits booths)
  - Complaints (e.g., competitors, HCPs, adverse event reports)
  - FDA "Bad Ad" Program and trade complaints

- FDA looks for:
  - Products:
    - Recurring violations
    - Consistent violative themes across different media
    - Level of public health risk
  - Companies:
    - Recurring violations across products
    - Evidence that company is "out of control"

Administrative Procedure Act (APA)

Administrative Procedures Act (APA) – Basic Principles

- Governs process FDA (and all agencies) uses to create rules and regulations that implement and enforce legislative acts
- Allows public participation in making of agency rules
  - Improve rules
  - Increase fairness
  - Judicial review
- Key Purpose: Transparency and Notice
  - Passed in 1946 in response to concerns that agencies were acting as fourth head of government without sufficient oversight or control
  - Works in tandem with Federal Freedom of Information Act

APA – Statutes versus Regulations versus Guidance

Statutes

- Passed by Congress
- Provide for broad social and economic goals and legal requirements – "guiding principles"
- Judicial review readily available for constitutionality

Regulations

- Issued by agencies
- Prescribe specific legal requirements to meet congressional goals
- Judicial review available but deference to agency can pose a challenge

FDA Guidance

- Represents FDA's current thinking on a topic – often in a new emerging area or where the statutes and regulations are unclear
- Does not establish legally enforceable responsibilities
- May use an alternate approach than what FDA recommends (unless otherwise required by statute/regulation) but has risk

APA – Due Process and Public Participation

- Must give notice of proposed rule
- Must take public comments and respond in final rule
- Regulations cannot be enforced if not published in the Federal Register
- Regulations cannot be effective until 30 days after publication
- Must publish statements of the organization and procedure for whom to contact for comment in the agency
- Must state the legal basis and purpose of the regulation

APA – Rulemaking Process

- Formal Rulemaking
  - "On-the-record" trial like process
  - Rarely used
- Informal Rulemaking
  - Used by most agencies
  - Basic Requirements:
    - Notice
    - Opportunity for comment
    - Statement of basis and purpose

APA – Rulemaking Process

- Regulation is proposed
- Office of Management and Budget reviews
- Proposed rule is published in the Federal Register
- Public comment is invited
- Office of Management and Budget re-reviews regulation
- Final regulation published in the Federal Register:
  - Must respond to comments
  - Amends Code of Federal Regulations
  - Sets effective date
    - 30-day minimum for most regulations
    - 60-day minimum for major regulations
    - No minimum for good cause
- Agency may delay or withdraw regulation before it becomes effective
- Agency submits regulation to Congress and Government Accounting Office,
- Regulation is placed in Code of Federal Regulations (CFR)

Key Takeaways

- FDA has broad authority over the development, manufacture, and marketing of drugs, biologics, and medical devices
- Understanding key FDA premarket and postmarket requirements is important to appropriately assess the risks and obligations associated with product development and marketing
- Failure to comply with FDA requirements can result in significant liability for companies and individuals
- Robust compliance and risk management strategies are necessary to ensure compliance throughout a product's lifecycle
- APA provides a backstop to unfettered FDA regulation and ensures public participation in rulemaking