Overview of FDA and Regulatory Processes

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FDLI

Agenda

- FDA Overview
  - Role in the federal government
  - Mission and structure
- Law and Policies
  - Statutes and regulations
  - Guidance documents and compliance policy guides
  - Enforcement
- Participation in Policy Making
- Product Specific Proceedings
- Information under the Freedom of Information Act (FOIA)

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FDA Overview

- Creation of FDA
  - Dr. Wiley's poison squad
  - Oldest and most comprehensive consumer safety agency
    - Origin as federal consumer safety agency began with the passage of the 1906 Pure Food and Drugs Act

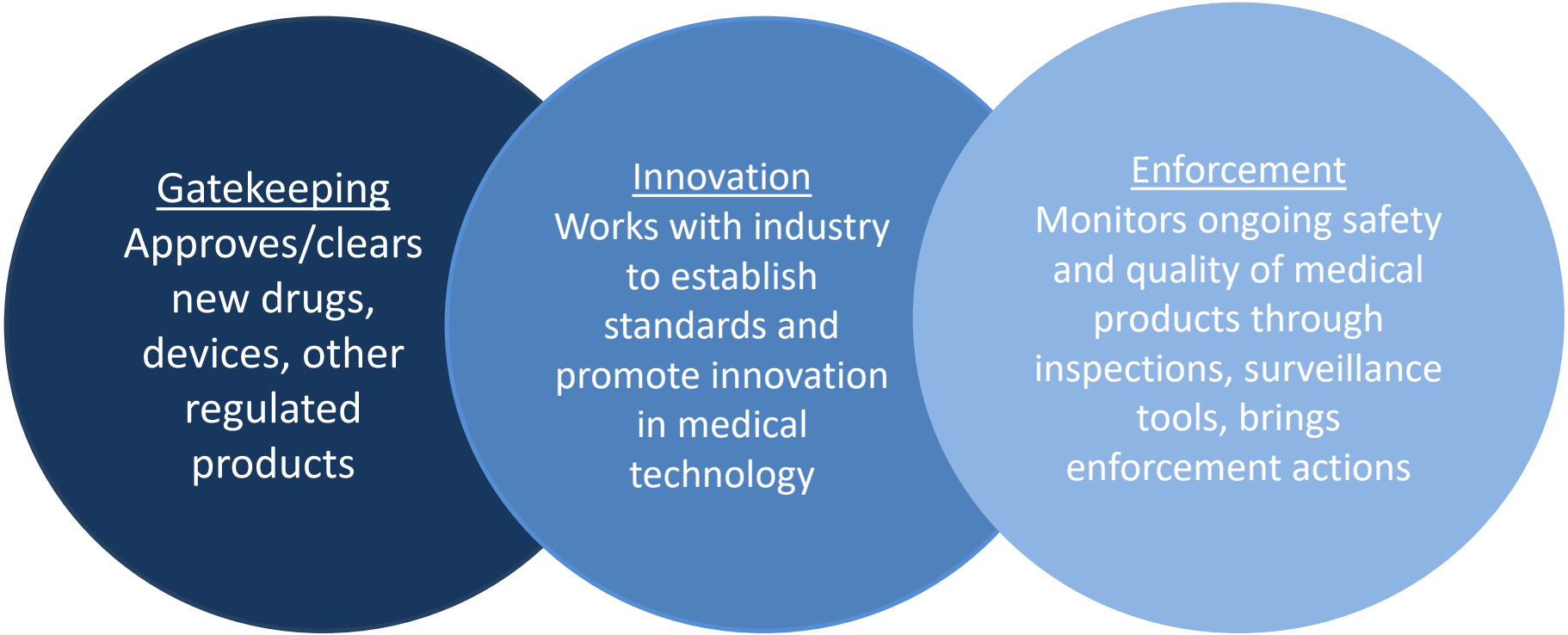
FDA Overview

- The Biologics Act of 1902
  - First law that implemented federal regulations of biological products such as vaccines and blood component products
- Federal Food, Drug and Cosmetic Act (FDCA) of 1938
  - Added definitions, prohibited acts, NDAs for “new drugs”, general recognition of safety (GRAS)
- Public Health Service Act (PHSA) of 1944
- Amendments of 1962
  - Added effectiveness, approval requirement, requirement for review of pre-1962 drugs
- Hatch-Waxman Amendments of 1984
  - Added ANDAs, market exclusivity, patent term extensions, and 505(b)(2) pathway

FDA Overview

- FDA Modernization Act of 1997
  - Action-forcing mechanisms
  - Repeal of outdated approval systems
  - Pediatric exclusivity
  - Registry of certain clinical trials
- Prescription Drug User Fee Act (PDUFA)
  - Registration fees
  - Performance targets
- FDA Amendments Act of 2007
  - REMS
  - Revised pediatric provisions
  - Safety labeling changes
  - Post-approval clinical trials
- Biologics Price Competition and Innovation Act (BPCIA)

FDA Overview



FDA Overview

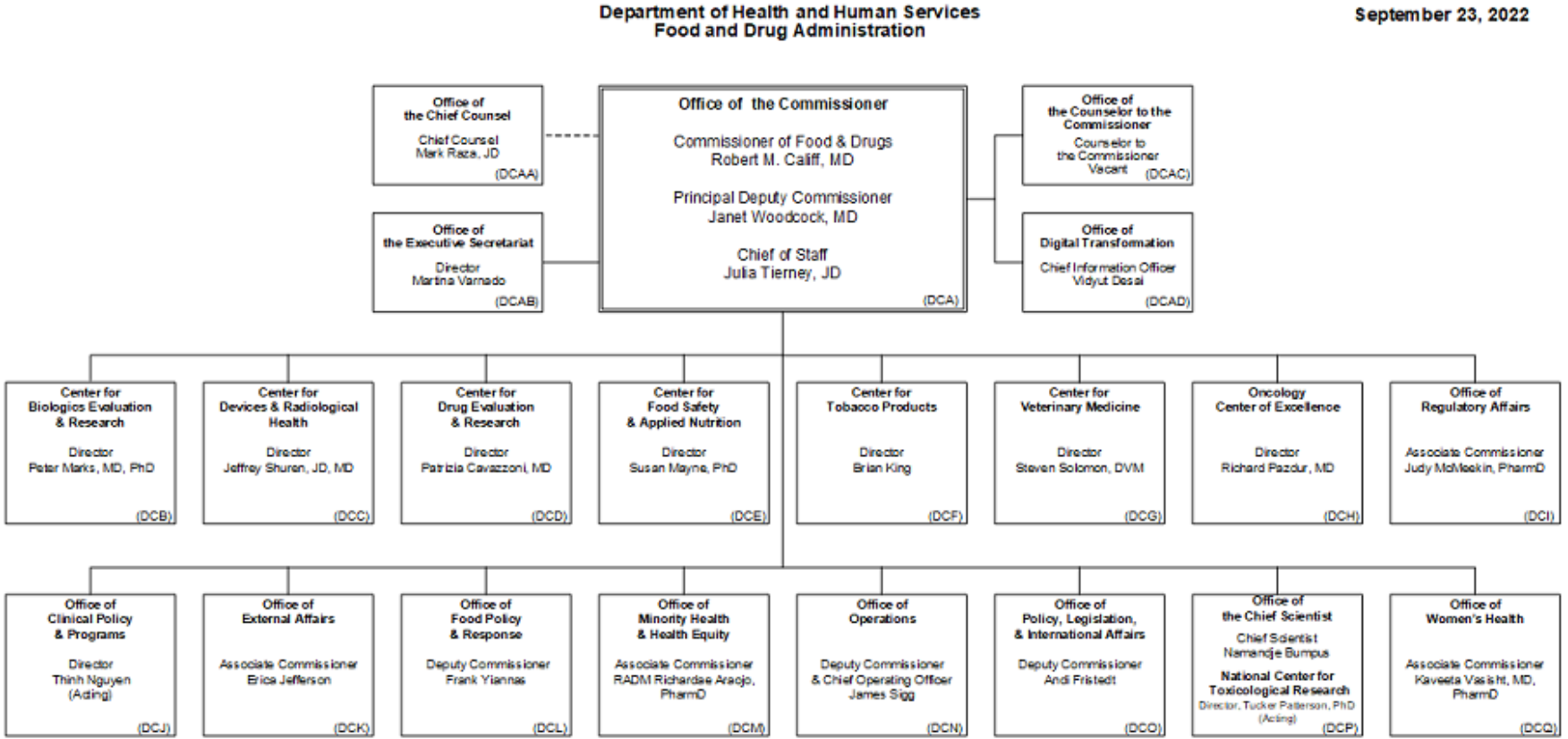
- Mission:
  - The Food and Drug Administration is responsible for protecting the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices; and by ensuring the safety of our nation's food supply, cosmetics, and products that emit radiation

FDA Overview

Department of Health & Human Services (HHS)

- Food & Drug Administration (FDA)
- National Institutes of Health (NIH)
- Centers for Disease Control & Prevention (CDC)
- Administration for Children & Families (ACF)
- Centers for Medicare & Medicaid Services (CMS)
- Office of Inspector General (OIG)

FDA Overview



FDA Overview

- CDER – Center for Drug Evaluation and Research
  - Regulates human drugs and some biologics
    - E.g., antibiotics, small molecule drugs, therapeutic biologics
- CBER – Center for Biologics Evaluation and Research
  - Regulates biologics and certain medical devices
    - E.g., vaccines, immunoglobulin products, some proteins produced by cell culture, some in vitro diagnostic products
- CDRH – Center for Devices and Radiological Health
  - Regulates the majority of medical devices
    - E.g., crutches, MRI machines, coronary stents

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FDA Law and Policies

Federal Food, Drug & Cosmetic Act (FDCA)

Public Health Service Act (PHSA)

Title 21 of the Code of Federal Regulations (CFR)

Guidance Documents

FDA Law and Policies

Topic	Drug Regulation	Biologics Regulation
INDs	Part 312	601.21 (Part 312 applies)
Marketing application content	314.50, 314.54, 314.94	601.2
Adverse Event Reporting	314.80	600.80
Deviation Reporting	314.81	600.14
Changes to approved application	314.70	601.12

FDA Law and Policies

- Rulemaking and explanations about FDA policy and procedures are in the Federal Register:
  - Publication of a document in the Federal Register generally provides public notice of its existence, specifies the legal authority of the agency to issue the document, and gives the document evidentiary status
  - For rulemaking documents, the Federal Register also shows how and when the CFR will be amended to include the new changes
  - The preamble discusses the background to the rule change, comments received, FDA's response to comments, and issues of interpretation

FDA Law and Policies

- Compliance Policy Guides (CPGs)
  - Explain FDA's policy on regulatory issues
  - Advise FDA's field inspection and compliance staff
  - E.g., chapter 4 is directed to human drugs and subchapter 400 describes FDA's enforcement policies with respect to marketing unapproved drugs
    - Higher priority for enforcement actions for unapproved drug products that have potential safety risks, lack evidence of effectiveness, health fraud drugs, etc.
- Manual of Policies and Procedures (MAPP)
  - Federal directives and documentation of internal policies and procedures

FDA Law and Policies

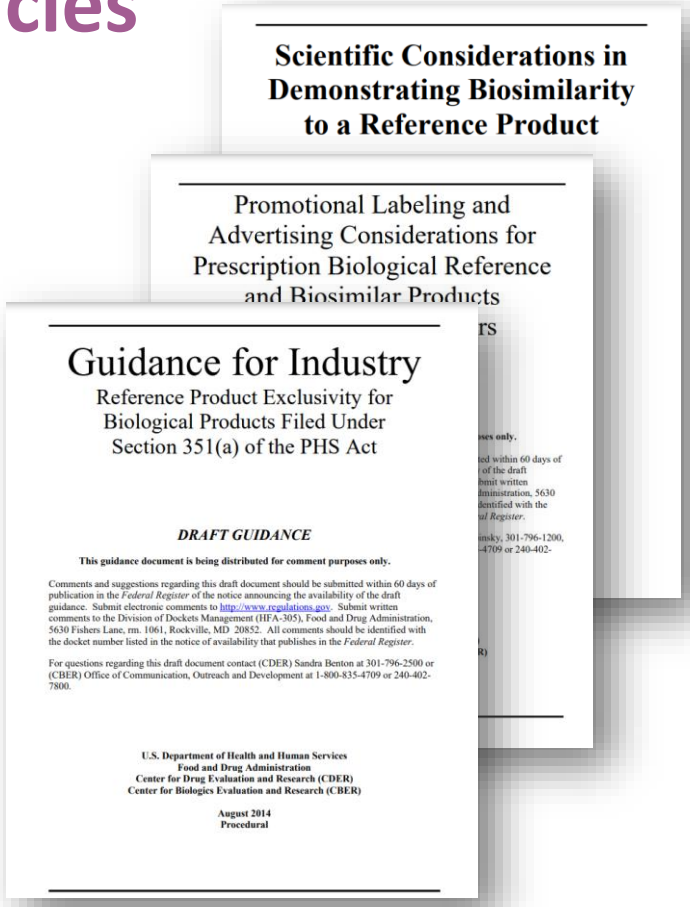
- Good Guidance Practices (GGPs)
  - E.g., 21 C.F.R. § 10.115
  - "FDA's policies and procedures for developing, issuing, and using guidance documents"
  - Soliciting and responding to public input, finalizing guidance documents
  - Must "be followed whenever regulatory expectations . . . not readily apparent from the statute or regulations are first communicated to a broad public audience"
  - Cannot use "other means of communication . . . to informally communicate new or different regulatory expectations to a broad public audience for the first time"

FDA Law and Policies

- Guidance documents
  - Draft guidances are **not** final guidances
    - Provide a good indication of FDA's thinking, but might change prior to finalization
  - Guidances (whether draft or final) are not binding, but provide FDA's current thinking and recommendations (not requirements)
  - Guidances contain a clear statement that the document is not binding and state that industry may use an alternative approach if the approach satisfies the requirements of the applicable statute and regulations
  - Cannot use binding language ("must," "shall," "required") in guidances unless referring to statutory or regulatory requirement

FDA Law and Policies

- Guidance documents
  - *Promotional Labeling and Advertising Considerations for Prescription Biological Reference and Biosimilar Products Q&A* (Feb. 2020)
  - *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (Apr. 2015)
  - *Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act* (Aug. 2014)



https://www.fda.gov/regulatory-information/search-fda-guidance-documents

FDA Law and Policies

- Enforcement – prohibited acts:
  - Adulteration (§ 501)
    - Failure to follow cGMPs
  - Misbranding (§ 502)
    - False/misleading labeling
    - No adequate directions for use
  - Unapproved new drug (§ 505(a))
    - No approved NDA or ANDA (biologics have own provision)
    - Failure to conform to final monograph/NDA (OTC)
  - Failure to maintain/make reports
  - Refusal to allow inspections

Prohibited act

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Interstate commerce

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Intent to defraud/mislead or second offense (for felony)

Formal enforcement authorities (criminal, seizure, injunction)

FDA Law and Policies

- Good manufacturing practices (GMP)
  - 21 C.F.R. §§ 210, 211
    - Qualified personnel
    - Quality control and quality assurance functions
    - Appropriate facilities and equipment
    - Laboratory controls
    - Recordkeeping
    - Validated processes
    - Failure investigations

FDA Law and Policies

- Advertising and promotion
  - Misbranding – FDCA § 502
    - Labeling is false or misleading
    - Labels/labeling lack required information or prominence
    - Failure to conform packaging and labeling to compendia
    - Advertisement lacks “true statement” in “brief summary” regarding side effects, contraindications, and effectiveness
    - Labeling lacks “adequate directions for use”

FDA Law and Policies

- Advertising and promotion

Basic Principles of Promotion
• Consistency with package insert (PI) • Fair balance • Substantiation • Not otherwise false or misleading • Promotional labeling must include PI (except reminder labeling) • Drug ads must include brief summary (except reminder ads) • Restricted device ads must include § 502(r) brief statement • Reporting on Form 2253 (drugs only)

FDA Law and Policies

- Enforcement mechanisms

Formal	Informal
• Prosecution • Seizures • Detentions • Injunctions • Consent decrees • Civil money penalties	• Warning letters • “Untitled” letters

FDA Law and Policies

- Criminal prosecution - § 303
  - Strict Liability
    - Felony if intentional or second offense
  - *Park/Dotterweich* Doctrine
    - Failure to exercise authority/supervision
    - Anyone in chain of responsibility
  - Prosecution not likely unless:
    - Intentional wrong
    - Serious public health issue
    - Continuing violation uncorrected with notice
    - But there is increased use of the *Park* Doctrine

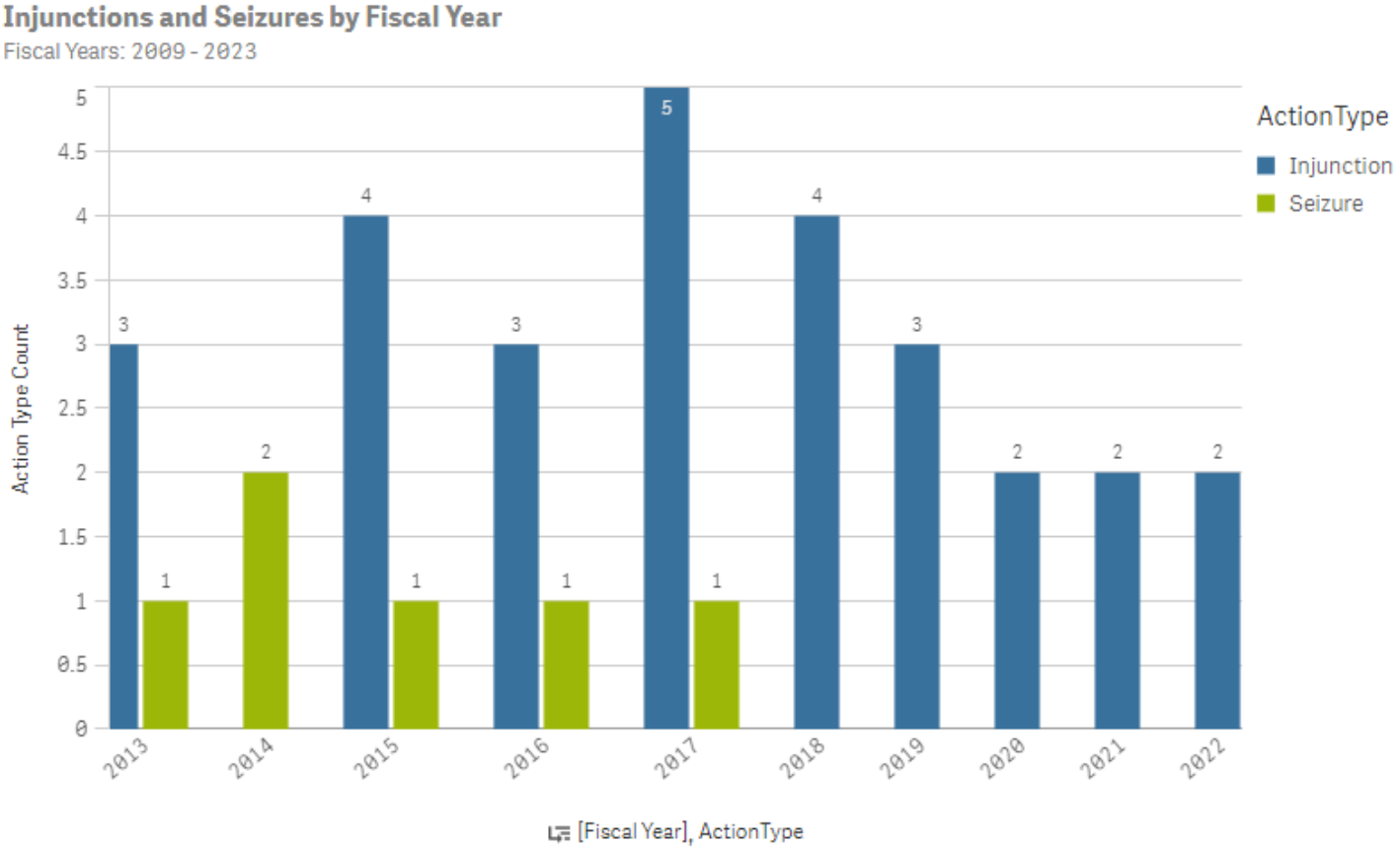
FDA Law and Policies

- Seizures - § 304
  - Arrest warrant to seize goods
    - Ex parte; no prior hearing
    - In rem admiralty rules (the product is the defendant)
  - Enjoins movement of seized articles
  - Followed by “condemnation” proceeding in U.S. District Court
  - Successful condemnation is followed by destruction, correction, or re-exportation

FDA Law and Policies

- Injunctions - § 302
  - Violation and possibility of recurrence
    - Stop violation
    - Affirmative requirements to prevent violation in the future
    - Continuing FDA/court/outside expert oversight
  - Individual defendants
  - Often resolved through consent decree
  - Penalty for violating injunction = contempt

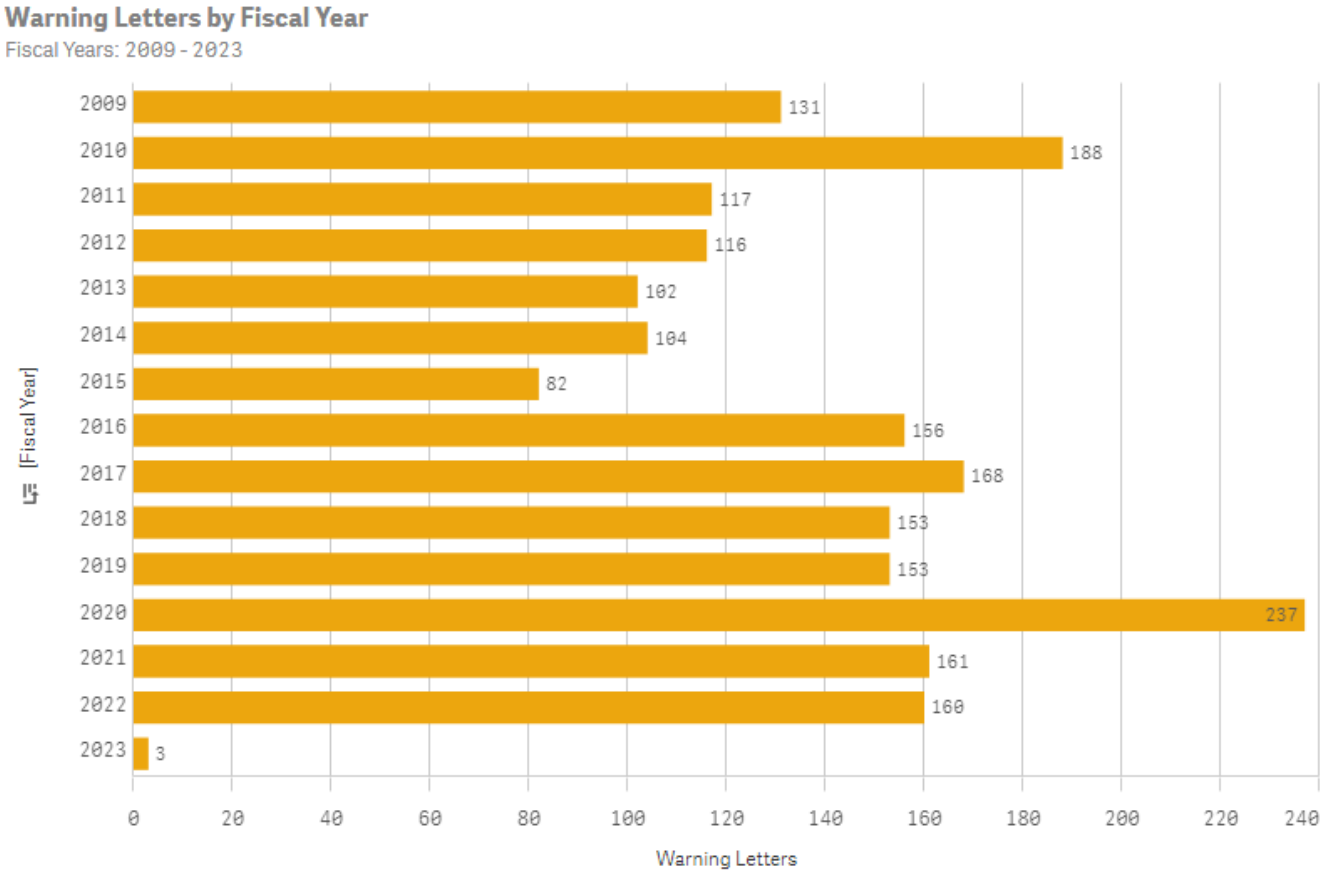
FDA Law and Policies



FDA Law and Policies

- Warning and “untitled” letters
  - Threat of enforcement action
  - May not represent final agency view but are taken seriously
  - Negative PR and may be used by competition
- Recalls
  - “Voluntary”
  - Expect an inspection

FDA Law and Policies



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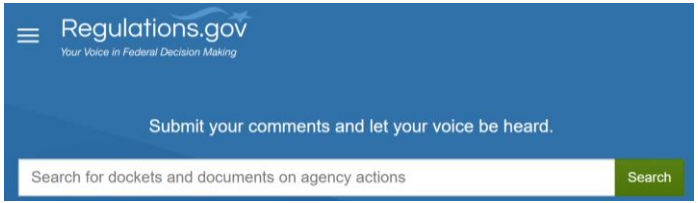
- Product Specific Proceedings
- Information under the Freedom of Information Act (FOIA)

Participation in FDA Policy Making

- Citizen petitions
- Comment on proposed regulations and draft guidance
- FDA meetings and workshops
- Advisory committee meetings
- Prescription Drug User Fee Act (PDUFA) and Biosimilar User Fee Act (BsUFA) negotiations
- Judicial review

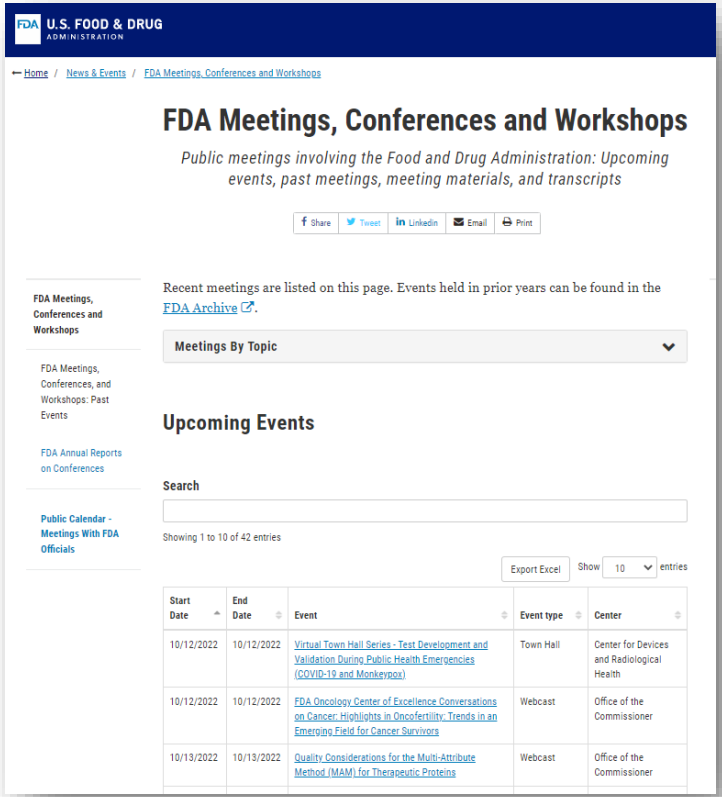
Participation in FDA Policy Making

- Comment on proposed regulations and draft guidance
  - 5 U.S.C. § 553 – rulemaking
    - Notice of proposed rulemaking shall be published in the Federal Register
    - "The agency shall give interested persons an opportunity to participate in the rule making through submission of written data, views, or arguments" and "after consideration of the relevant matter presented, the agency shall incorporate in the rules adopted a concise general statement of their basis and purpose."



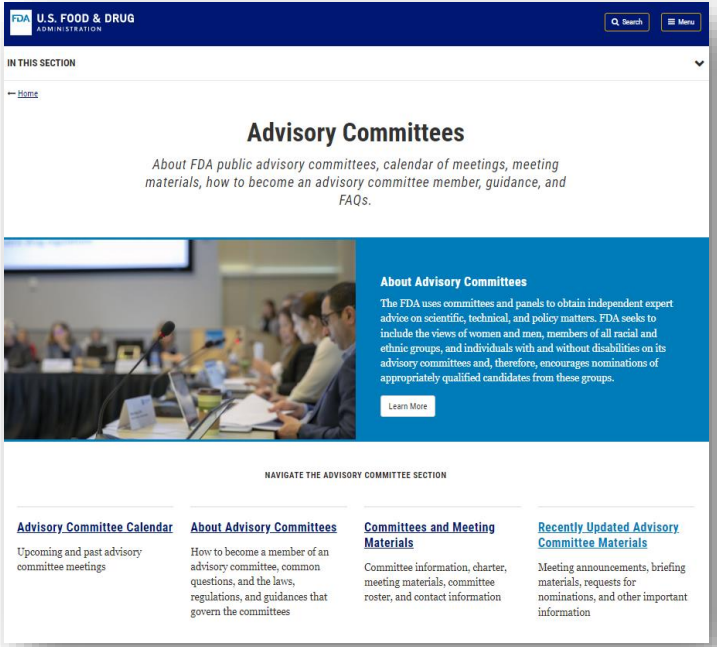
Participation in FDA Policy Making

- FDA meetings and workshops
  - FDA publishes upcoming events on their website
  - Presentations, background materials, and transcripts are available for these events



Participation in FDA Policy Making

- Advisory committee meetings
  - Publication in the Federal Register at least 15 days before a meeting
  - Registration required if you plan to speak during the open public hearing portion of the meeting
  - Used to obtain independent expert advice on scientific, technical, and policy matters



Participation in FDA Policy Making

- Prescription Drug User Fee Act (PDUFA) and Biosimilar User Fee Act (BsUFA) negotiations
  - 6th reauthorization of PDUFA
    - PDUFA VII Commitment Letter
  - 2nd reauthorization of BsUFA
    - BsUFA III Commitment Letter

Participation in FDA Policy Making

- Judicial review
  - *Chevron v. NRDC* two-step
    - (1) Has Congress directly addressed the question at issue?
    - (2) If not, is the agency's interpretation based on a permissible construction of the statute?
  - *Skidmore v. Swift* factors
    - Thoroughness, validity, consistency, and persuasiveness
  - *United States v. Mead*
    - *Chevron* deference generally applies to formal adjudications and notice-and-comment rulemaking
    - *Skidmore* deference generally applies to policy statements, agency manuals, enforcement guidelines, and similar agency actions
  - *Auer v. Robbins*
    - Courts generally will uphold agency interpretations (even informal) of its own rule unless it is "plainly erroneous or inconsistent with the regulation"

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Product Specific Proceedings

- Dispute resolution
  - Discuss with product review team and the division or office director, as appropriate
  - Ombudsman – “FDA is committed to the principle that regulated industry has a right to disagree with an agency decision, action, or operation, and that full and open discussion of issues in controversy produces a better decision in the end.”
  - Formal dispute resolution (21 C.F.R. § 10.75)
  - Petition for reconsideration (21 C.F.R. § 10.33)
  - Litigation

Product Specific Proceedings

- Citizen petitions
  - 21 C.F.R. § 10.30
  - Request that FDA take specific action
    - E.g., impose new/additional criteria for approval of ANDAs for public health/safety reasons
  - Petition is public and is placed on a public docket
  - FDA has 180 days to respond (no extensions)

Product Specific Proceedings

- Citizen petitions
  - Procedural provisions were added in 2007 to counter “misuse” of the citizen petition process:
    - FDA may not delay the approval of pending ANDAs unless it makes a formal determination that a “delay is necessary to protect the public health”
    - FDA is required to notify an ANDA applicant within 30 days of such a determination and identify additional information needed to resolve the issues raised in the petition
    - FDA may deny a petition at any time if it finds the petition was submitted with the “primary purpose of delaying an application” and “the petition does not on its face raise valid scientific or regulatory issues”

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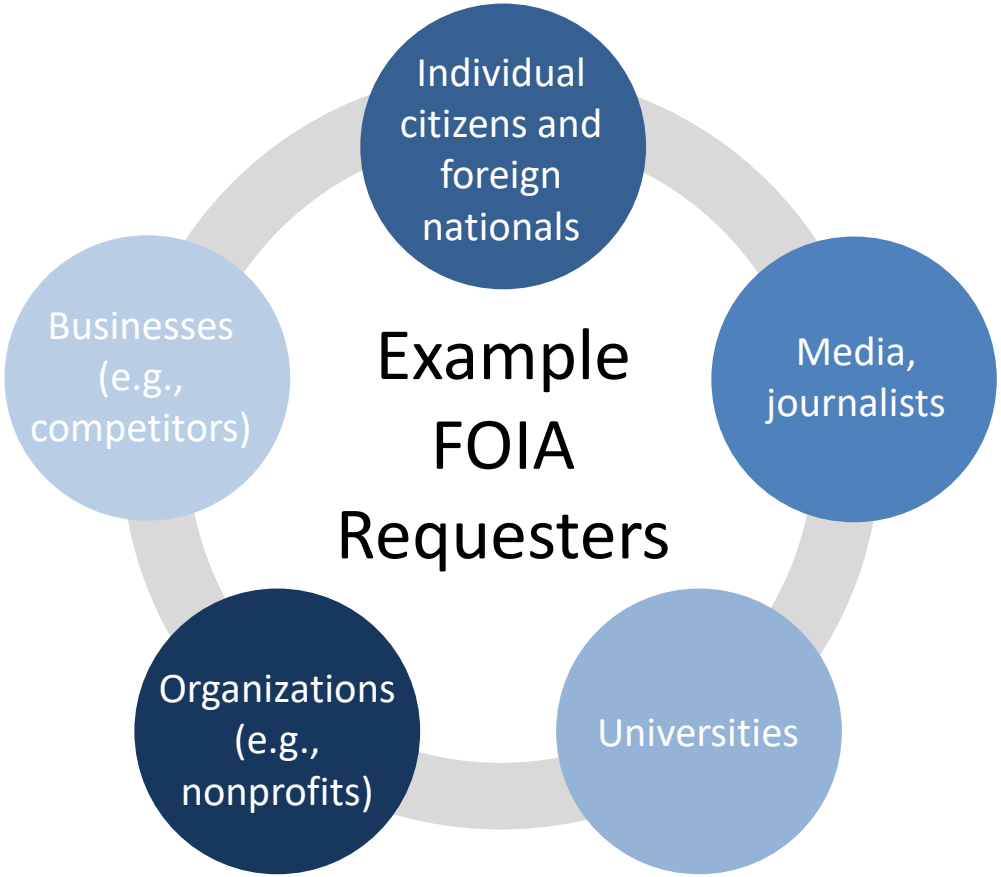
Obtaining and Protecting Info Under FOIA

- The Freedom of Information Act (FOIA) (5 U.S.C. § 552) requires federal government agencies to make records publicly available upon request
  - Enacted in 1966
  - 21 C.F.R. Part 20 and § 314.430
  - There is a general presumption under FOIA in favor of disclosure of the requested material

Obtaining and Protecting Info Under FOIA



Obtaining and Protecting Info Under FOIA

- 5 U.S.C. § 552(a): Each agency shall make available to the public information as follows:
  - Substantive rules and statements of policy of general applicability
  - Opinions and orders in adjudication of cases
  - Unpublished statements of policies
  - Records per a request that reasonably describes the records
- 5 U.S.C. § 552(b): This section does not apply to matters that are:
  - Trade secret information or confidential commercial or financial information obtained from a person and is privileged or confidential
  - Personnel and medical files
  - Records compiled for law enforcement purposes or relating to ongoing enforcement investigations (§ 552(c))

Obtaining and Protecting Info Under FOIA

- FOIA exemptions:
  - (1) Classified Documents
  - (2) Internal Personnel Rules and Practices
  - (3) Records Exempted by Other Statutes
  - **(4) Confidential Business Information**
  - (5) Privileged from Disclosure in Litigation
  - (6) Personal Privacy
  - (7) Law Enforcement Records
  - (8) Financial Institutions
  - (9) Geological Information

Obtaining and Protecting Info Under FOIA

Trade Secret Information	Commercial or Financial Information
A trade secret may consist of any commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding, or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort. There must be a **direct relationship between the trade secret and the productive process**.	Commercial or financial information that is privileged or confidential means valuable data or information which is used in one's business and is of a type **customarily held in strict confidence or regarded as privileged and not disclosed to any member of the public** by the person to whom it belongs.

Obtaining and Protecting Info Under FOIA

- Confidential commercial information is generally protected from disclosure if the submitter has a “commercial interest” in the information and if there is competitive harm
- Confidentiality test:
  - (1) the information is customarily and actually kept private, or at least closely held, by the submitter; and
  - (2) the government provides some assurance that the information will not be publicly disclosed

Obtaining and Protecting Info Under FOIA

- Trade secret information includes product manufacturing and design information:
  - Product specifications
  - Certificates of analysis and other test results
  - Manufacturing facility information
  - Manufacturing processes
- Trade secret information excludes general information that would be typical of a product of that type or that reflects established industry practices

Obtaining and Protecting Info Under FOIA

- Requester submits request for information to a federal agency
- Regulations provide that the agency must determine and state within 20 business days after receipt of request whether it will comply and provide rationale if not
  - Actual response time is usually much longer
  - But, the DC Circuit has held that documents must be produced within "days or weeks of a determination, not months or years"
- If requested records include information submitted by a private entity, the agency must provide notice to the submitter and an opportunity to object to disclosure of the information
- Agency determination to release or withhold records is subject to judicial challenge from the submitter of information and requester

Obtaining and Protecting Info Under FOIA

- Reverse FOIA litigation
  - This type of litigation occurs when the submitter of information – usually a corporation or other business entity that has supplied an agency with data on its policies, operations or products – seeks to prevent the agency that collected the information from revealing it to a third party in response to the third party's FOIA request
  - Agency rationale:
    - None of the FOIA exemptions apply and disclosure is mandatory;
    - One or more of the FOIA exemptions apply, but disclosure is justified in the exercise of the agency's discretion

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