Introduction to Drug Law and Regulation: Origins and Overview of the FDA and the Regulation of Drugs

FDLI - Introduction to Drug Law and Regulation
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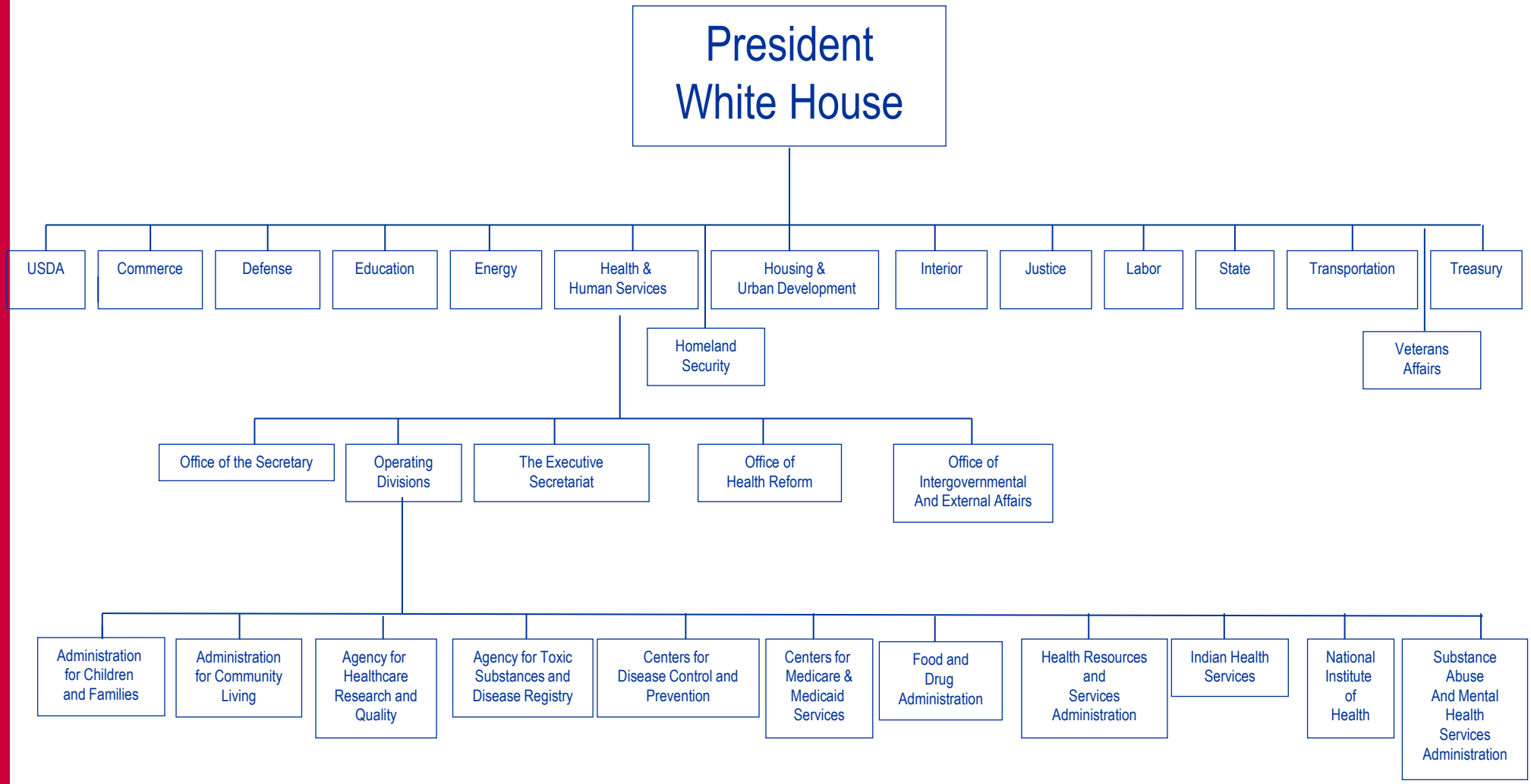
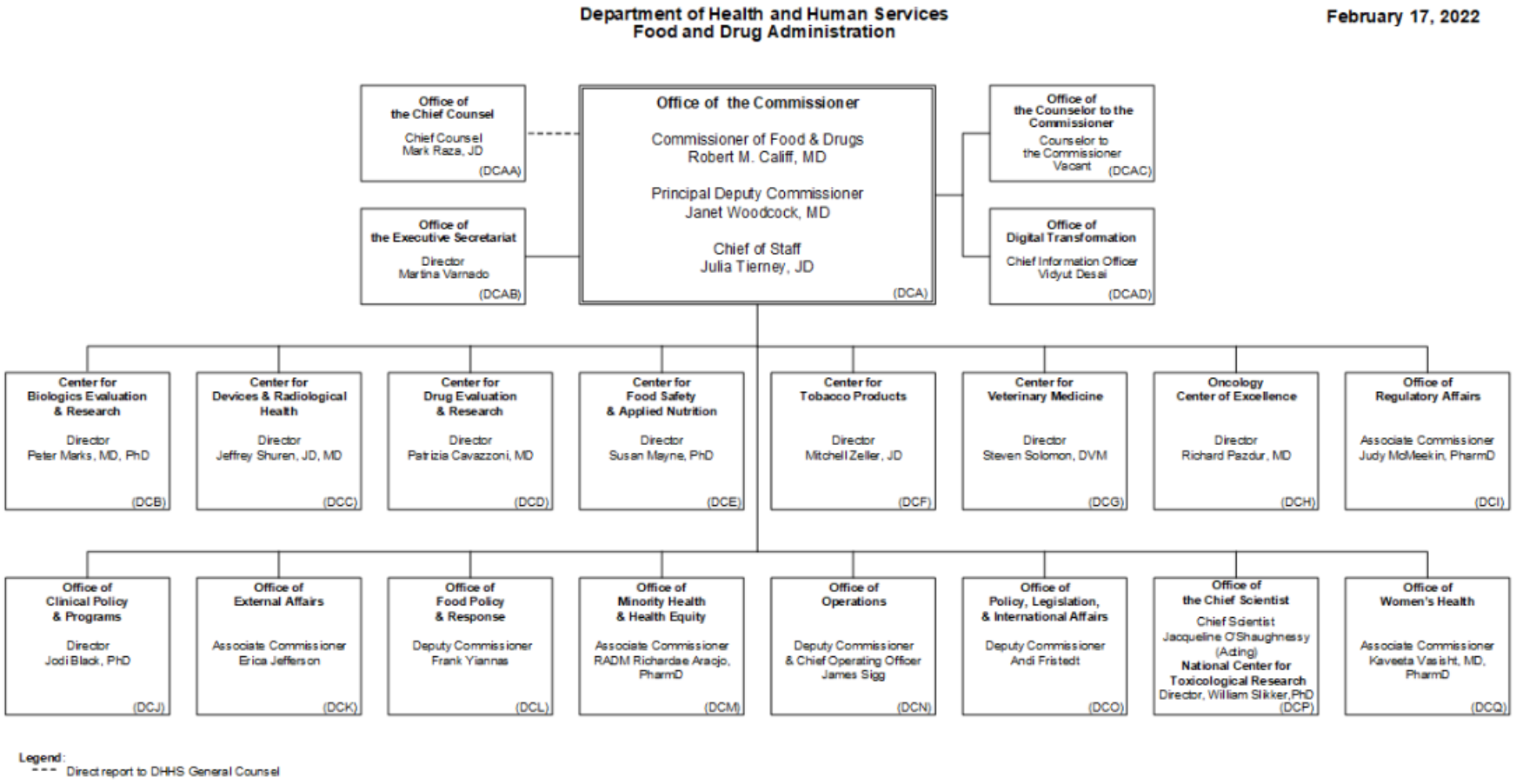
Topics

1. Historical Context/FDA's Place in Government
2. Major Statutory Underpinnings of Today's Framework
3. Sources of Legal and Regulatory Requirements and FDA Policies
4. Participating in FDA Policymaking
5. Product-Specific Regulatory Proceedings

FDA in the Executive Branch



Department of Health and Human Services
FDA



Federal Food, Drug, and Cosmetic Act of 1938

- Premarket review of New Drug Applications (NDAs)
- Drugs must be safe and labeled with adequate directions for use
- Brought cosmetics and medical devices under FDA control
- Kept control of drug advertising under FTC

Durham-Humphrey Amendment of 1951

- Defined two specific categories for medications: legend (prescription) and OTC. A drug could not be both

- Prescription:
  - Habit forming;
  - Unsafe without medical supervision; and/or
  - Subject to NDA process

Thalidomide

- Marketed for nausea in other countries
- Caused thousands of birth defects and deaths

Frances Oldham Kelsey

The 1962 Drug Amendments/Kefauver-Harris Act

- Premarket notification replaced by premarket approval, based on a demonstration of both safety and efficacy

- Expanded FDA's authorities with respect to Good Manufacturing Practices, drug labeling, clinical trials, and access to records

Drug Efficacy Study Implementation (DESI) Review

- Program to evaluate the efficacy of approved pre-1962 drugs
- Created scientific panels that classified drugs as effective, ineffective or requiring further scientific information
- DESI drugs and identical, related, or similar products could remain on the market during the process

Over-the-Counter (OTC) Drug Review

- FDA allows drugs that are safe and effective for use by the general public without prescription to be sold OTC
- Review program launched in 1972 to evaluate safety and efficacy of pre-1972 OTC drugs.
- Evaluated whether ingredients were generally recognized as safe and effective (GRASE) for use in self-treatment
- Public rulemaking to establish monographs setting forth conditions under which OTC drugs are GRASE
- Monograph system overhauled in 2020

Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch Waxman)

- Created the Abbreviated New Drug Approval (ANDA) generic drug pathway under section 505(j) of the FDCA
- Created 505(b)(2) pathway for NDAs
- Created periods of “regulatory exclusivity” that protect an approved drug from competing applications for marketing approval under specified conditions

NDA vs. ANDA Review Process

Brand Name Drug NDA Requirements	General Drug ANDA Requirements
1. Chemistry	1. Chemistry
2. Manufacturing	2. Manufacturing
3. Controls	3. Controls
4. Labeling	4. Labeling
5. Testing	5. Testing
6. Animal Studies	
7. Clinical Studies	6. Bioequivalence
8. Bioavailability	

Prescription Drug Marketing Act of 1987

- Established a legal framework for the safe and effective distribution of prescription drugs
- Prohibits the sale, purchase, or trade of prescription drug samples or coupons
- permit only the U.S. manufacturer of a drug to reimport such drug into the United States, except for emergency medical care

Drug User Fee Programs

- Prescription Drug User Fee Act of 1992 (PDUFA)
- Generic Drug User Fee Amendments (GDUFA)
- Over-The Counter Monograph Drug User Fee Program (OMUFA)
- Allows FDA to collect user fees from drug and biologics manufacturers
- Sets performance goals
- Renegotiated and reauthorized every 5 years

Modern Statutory Underpinnings

- FDA Safety and Innovation Act (2012)
  - Reauthorized PDUFA/GDUFA fees and created fees for biosimilars
  - Section 907: implemented Inclusion of Demographic Subgroups in Clinical Trials
- Drug Quality and Security Act (2013)
  - Requires electronic tracing of drug products at package level
  - Enhanced licensure standards
  - Notifications to FDA of illegitimate products
  - Set a formal program for FDA regulation of compounded drugs
- 21st Century Cures Act (2016)
  - Increased agency budget
  - Expanded access requirement

Modern Statutory Underpinnings (continued)

- FDA Reauthorization Act (2017)
  - Reauthorized user fee programs
  - Created priority review pathway for ANDAs of drugs on FDA shortage list
  - required FDA to publish an updated list of all drugs for which all patents and periods of exclusivity have expired, and for which FDA has not approved an ANDA referencing the product
- The Coronavirus Aid, Relief, and Economic Security Act (2020)
  - Created reporting obligation for drug and API shortages
  - Created new administrative process for OTC monographs.

Sources of Legal and Regulatory Requirements and FDA Policies

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Sources of Legal and Regulatory Requirements and FDA Policies

- Constitution
- Statutes
- Regulations
- Federal Register Notices
- Advisory Committees
- Guidance Documents
- Compliance Policy Guides
- Staff Manuals
- Memoranda of Understanding
- Enforcement actions and letters
- Informal statements and advice

Statutes

- Federal Food, Drug, and Cosmetic Act (21 U.S.C. § 301 et seq.)
  - Establishes FDA's regulatory authority over drugs, including biological products which meet the definition of "drugs" under FDCA § 201(g)
- Public Health Service Act (42 U.S.C. § 201 et seq.)
- Administrative Procedures Act (5 U.S.C. § 500 et seq.)
- Constitutional limits

Regulations

- FDA regulations are binding and issued under statutory authority.
  - "A valid legislative rule is binding upon all persons, and on the courts, to the same extent as a congressional statute. When Congress delegates rulemaking authority to an agency, and the agency adopts legislative rules, the agency stands in the place of Congress and makes law." *National Latino Media Coalition v. Federal Communications Commission*, 816 F.2d 785, 788 (D.C. Cir. 1987)

- A regulatory agency's issuance of a regulation requires "notice and comment" rulemaking under the APA.
  - FDA issues a notice of proposed regulation in the Federal Register and includes a deadline for submission of public comments
  - Following comments, FDA may issue a final rule, including information regarding the basis and purpose of the rule

Federal Register Notices

- The Federal Register is the official journal of the federal government
  - Available in print or online at www.federalregister.gov
- The Federal Register is issued on a daily basis for all federal agencies, and covers many topics, including:
  - Proposed and final regulation
  - Administrative guidance
  - Agency determination
  - Enforcement decisions

FEDERAL REGISTER
The Daily Journal of the United States Government

Regulation Preambles

- A regulation preamble is the text that precedes the regulation in the Federal Register
- Preambles are not binding
- They explain FDA's thinking behind the regulation, discuss the impact of the rule, and may address comments from the public
- The preamble of a final rule contains the statement of "basis and purpose" of a regulation as required by the APA.

Advisory Opinions

- An advisory opinion represents the formal position of FDA on a matter and obligates the agency to follow it until it is amended or revoked. (21 C.F.R. § 10.85)
- FDA established advisory opinions as a formal mechanism by which "any person could request and advisory opinion from the Commissioner with respect to any matter of general applicability." 42 Fed. Reg. 4680,4708 (1977)
- Includes Compliance Policy Guides
- FDA may not recommend legal action against a person or product for action taken in conformity with an advisory opinion

Guidance Documents and Good Guidance Practices

- FDA guidance describes the agency's current thinking on regulation or a statute and are aimed at industry and agency staff
- Not binding
- Explain FDA's interpretation of, or policy regarding, statutory or regulatory issues
- FDA maintains policies and procedures for the development of guidance documents, known as Good Guidance Practices (21 C.F.R. § 10.115)

Compliance Policy Guides

- Compliance Policy Guides (CPGs) explain policy on regulatory issues related to FDA laws or regulations.
- Advise FDA's field inspection and compliance staffs, as well as the industry, as to the Agency's strategy and policies to be applied when determining industry compliance.
- Tend to be very issue-specific

Staff Manuals Guides and Manuals

- FDA issues Staff Manual Guides (SMGs) and Manuals of Policies and Procedures (MAPPs) internally
- SMGs are the Agency directives that document organizations and functions; delegations of authority; and administrative and program policies, responsibilities and procedures.
- MAPPs are required by law and made available to the public to make FDA a more transparent organization

Enforcement Actions and Letters

- Warning letter
  - Issued when FDA finds significant violations and publicly available
  - Requires response within 15 business days with a plan for corrective action
  - Failure to take corrective action may result in enforcement such as seizures, recalls, or import detention
- Untitled Letter
  - Cites violations that may not meet the threshold of significance for a Warning Letter.
  - Not accessible through a central database. May be obtained through FOIA request.

Citizen Petition Responses

- Citizen petitions are formal requests to FDA, asking the Agency to take or refrain from certain action (21 CFR § 10.30)
  - E.g., requesting that FDA deny a competitor's marketing application
- Under FDASIA, FDA is required by law to respond to Citizen Petitions within 150 days, but rarely meets the deadline
- Citizen petition responses may provide insight into FDA's regulatory interpretations

Informal Statements and Advice

- Informal advice through email, telephone, etc.
- FDA website
- FDA webinars
- Formal meeting requests between FDA and sponsors or applicants
  - Reserved for products subject to user fees
  - Type A, B, or C meeting
  - Guidances on the principles of good meeting management practices

Obtaining and protecting information under the Freedom of Information Act (FOIA)

- The Freedom of Information Act, or FOIA (5 U.S.C. § 522), generally provides that any person has the right to request access to agency records, to the extent the records are not protected from disclosure by statutory exemptions

  – FDA's FOIA regulations are codified in 21 C.F.R. Part 20, and mirror the statutory provisions

  – FOIA requests must be specific enough to permit an FDA employee who is familiar with the subject matter to locate records in a reasonable period of time

  – FDA may charge a fee for processing a FOIA request

  – Certain records may be withheld in whole or in part from the requestor if they fall within one of nine FOIA exemptions.

Obtaining and protecting information under the Freedom of Information Act (FOIA)

- A stakeholder may attempt to prevent or challenge disclosure under FOIA

  –designate all or part of a record as FOIA exempt in writing

  – If notified by FDA that the record may be subject to disclosure, the submitted will have 5 working days to object and provide justification

  – If FDA overrules the objection, the submitted may challenge the decision in court

Participating in FDA Policymaking

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Citizen Petitions

- Citizen petitions are formal requests to FDA, asking the Agency to take or refrain from certain action (21 CFR § 10.30)
- Citizen petitions have specific content and formatting requirements
- Under FDASIA, FDA is required by law to respond to Citizen Petitions within 150 days, but rarely meets the deadline
- Citizen petitions can be subject to antitrust scrutiny, and FDA can refer “sham” petitions to the FTC for enforcement action

Rule-Making Comments and Hearings

- To issue regulations, FDA goes through the “notice and comment rulemaking” process
  - Advance notice of proposed rulemaking (ANPRM)
  - Notice of proposed Rulemaking (NPRM)
  - Public comment period (regulations.gov)
  - Agency decision
- FDA also solicits comments on draft guidance documents when they are published in the federal register

Public Meetings

- FDA hosts frequent public meetings and online webinars
  - Advisory committee and panel meetings to request expert advice on regulatory or scientific issues
  - Public meetings, conferences and workshops
  - Minutes, transcripts, summaries and/or presentations for FDA-sponsored or co-sponsored meetings and workshops are made available on FDA's website.

Product-Specific Regulatory Proceedings

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Informal Dispute Resolution

- Scientific or procedural disputes between FDA and sponsors may arise during product development, application review, and/or post-marketing
- FDA strongly suggests that sponsor first discuss it with the review team and Division/Office Director, as appropriate.
- Sponsors can request a formal meeting to seek resolution
  - Type A: necessary for an otherwise stalled product development program to proceed or to address an important safety issue.
  - Type B: can be requested for both pre- and post-approval matters
  - Type B (EOP): End-of-Phase meetings.
  - Type C: Any other meeting regarding the development and review of a product

Formal Dispute Resolution

- Stakeholders can seek formal dispute resolution through supervisory review up the chain of command (21 C.F.R. § 10.75)
- Sponsor may request review of scientific controversy by an advisory committee
- Internal agency review of a decision must be based on the information in the administrative file
- Sponsors submit formal written requests, which FDA will direct to the appropriate official for review
- After review, will send written response agreeing or disagreeing with bases for decision
- For disputes regarding applications covered by a user fee act, FDA attempts to respond within 30 calendar days

Regulatory Hearings

- FDA may decide to offer opportunity for regulatory hearing when considering regulatory action (or inaction) (21 C.F.R. Part 16)
- Particular statutory or regulatory provisions may provide interested person opportunity for regulatory hearing
- Initiated by “notice of opportunity for a hearing” from FDA
- Notice will specify time within which hearing may be requested

Regulatory Hearings

- Public hearing, unless FDA determines hearings should be closed
- Generally presided over by FDA employee or administrative law judge that will write a post-hearing report
- Commissioner issues final written decision based on administrative record of the hearing
- Party may petition FDA for reconsideration or for stay of decision or action

Judicial Review

- Under the Administrative Procedure Act, courts can only review agency actions when they are “final.”
- FDCA also provides for direct judicial review of certain product specific Agency orders and regulations at the request of persons adversely affected by such orders or regulations
- Judicial review of administrative action is rare and typically results in a decision that yields to an agency's interpretation of either a statute that Congress instructed the agency to administer or a regulation promulgated by the agency

Questions?

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