Introduction to Drug Law and Regulation: Overview of Drug Law and Regulation

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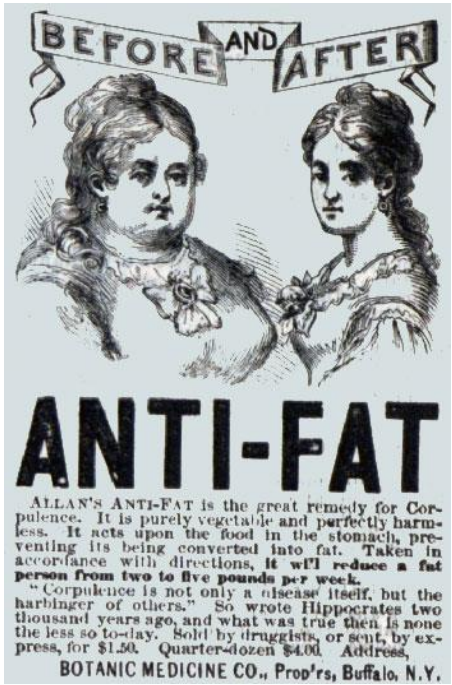
Topics

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

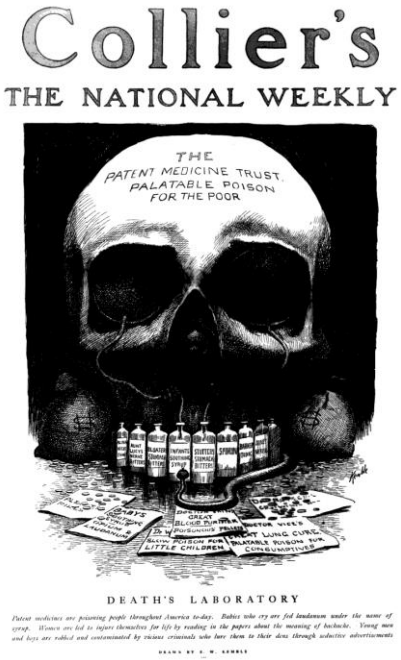
Developments Leading to Federal Regulation of Drugs

- Limited federal regulation of drugs in the 19th century
  - e.g., statutes related to foreign commerce in food and drugs and safe and effective smallpox vaccine
- Proliferation of public food markets and patent medicines
  - Typically no listed ingredients, warnings or precautions
  - Minimal testing for adulteration, contamination, dilution



Developments Leading to Federal Regulation of Drugs

- USDA Chief Chemist Dr. Harvey Wiley
  - Investigated and published information regarding food and drug adulteration
  - Conducted “hygienic table studies,” testing the effects of chemicals and adulterated foods on the so-called “poison squad”
    - Borax
    - Formaldehyde
    - Salicylic acid
    - Sulfuric acid
    - Sodium benzoate
- Public attention on food and drug adulteration
  - Upton Sinclair’s *The Jungle*
  - Muckraking journalism



Early Federal Statutes

- Biologics Control Act of 1902
  - Established federal body with licensure authority over establishments producing and distributing biological products
  - Passed in response to distribution of tetanus-contaminated vaccines resulting in deaths of 22 children

- 1906 Food and Drugs Act
  - Prohibited introduction into interstate commerce of misbranded or adulterated food and drugs
  - Regulation based on product labeling
  - No premarket approval provisions

Elixir Sulfanilamide

- Elixir sulfanilamide tragedy resulted in more than 100 deaths, many of which were pediatric deaths
  - Elixir sulfanilamide marketed in a liquid form for the treatment of strep infections
  - Contained diethylene glycol (widely used as automotive antifreeze)

Federal Food, Drug, and Cosmetic Act of 1938

- Premarket review of New Drug Applications (NDAs)
  - Under 1938 statute, NDA would automatically become effective after 60 days absent FDA disapproval

Thalidomide

- Thalidomide, marketed for morning sickness in pregnant women, found to be a teratogen, resulting in birth defects

- At the time, thalidomide NDA was pending in the United States

Drug Amendments of 1962/Kefauver-Harris Act

- Premarket notification replaced by premarket approval, based on a demonstration of safety *and* efficacy
  - Required sponsors to demonstrate the efficacy through data from adequate and well-controlled clinical trials
  - Previously, FDA could exercise authority over therapeutic claims pursuant to its misbranding authorities

- Also 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 pre-1962 drugs already on the market
  - Intended to classify drugs as effective, ineffective, or requiring further study
- FDA permits drugs subject to an open DESI proceeding to remain on the market

Over-the-Counter (OTC) Drug Review

- FDA may permit marketing of drugs that are safe and effective for use by the general public without prescription to be sold OTC

- OTC Drug Review
  - Established to evaluate the safety and effectiveness of OTC drug products marketed prior to May 11, 1972
  - Evaluate whether ingredients could be generally recognized as safe and effective (GRASE) for use in self-treatment
  - Public rulemaking process to establish monographs describing conditions under which certain OTC drugs are GRASE

- Ways to obtain OTC status
  - Compliance with published OTC monograph
  - Approved NDA or ANDA
  - Switch to OTC status by regulation or sNDA

Drug Price Competition and Patent Term Restoration Act of 1984

- Commonly referred to as Hatch-Waxman
- Balances encouraging development of generic drugs with incentives for “pioneer” drug innovation
- Abbreviated approval pathways for generic drugs
  - Abbreviated New Drug Application (ANDAs)
  - 505(b)(2) New Drug Application

Hatch-Waxman (cont.)

- Abbreviated approval pathways for generic drugs
  - Abbreviated New Drug Application (ANDAs)
    - Applicant must demonstrate bioequivalence to the reference listed drug (RLD)
    - Product must generally have the same route of administration, dosage form, strength, labeling, and intended use
  - 505(b)(2) New Drug Application
    - Allows application to rely on information for which the applicant has not obtained a right of reference
    - Product may differ from RLD in certain respects (e.g., different route of administration, dosage, strength)

Hatch-Waxman (cont.)

- Provides for patent term extension
  - Patent may be extended for a portion of the development and review period (half the time between IND application and NDA submission, plus NDA review time)
  - Remaining term of the restored patent is not to exceed 14 years

- Created certain non-patent exclusivities:
  - 5-year New Chemical Entity (NCE) exclusivity
    - FDA is not permitted to accept an ANDA or 505(b)(2) application for the same drug for a period of 5 years (or 4 years with a paragraph IV certification to a listed patent)
  - 3-year Clinical study exclusivity
    - 3-year exclusivity period for NDA containing new clinical studies essential for approval, preventing FDA from approving any ANDA or 505(b)(2) application relying on that approval
  - 180-day exclusivity
    - 180-day exclusivity period for the first generic applicant challenging a listed patent (by filing a paragraph IV certification)

Prescription Drug User Fee Act (PDUFA) of 1992

- Allowed FDA to collect user fees from drug and biologics manufacturers
  - Collected for product applications, supplements, and other submissions
- Created FDA performance goals for review
- Renegotiated and reauthorized every 5 years

Public Health Service Act (PHSA) of 1944

- Premarket approval framework for biologics intended for human use via Biologics License Applications (BLAs)
  - Based on a demonstration that the product is “safe, pure, and potent”
  - Biological products are derived from living organisms and have more complex structures than small molecule drugs (e.g., vaccines, blood and blood components, cellular and tissue based products)

Biologics Price Competition and Innovation Act of 2009

- Abbreviated approval pathway for follow-on biologics that are “biosimilar” to or “interchangeable” with a reference product
  - “Biosimilar” – “highly similar” to the reference product with “no clinically meaningful differences” in safety, purity, and potency
  - “Interchangeable” – a biosimilar product which “may be substituted for the reference product without the intervention of the healthcare provider who prescribed the product”

- Exclusivities and patent dispute procedures
  - 12-year exclusivity for reference products (no follow-on applications until 4 years from first licensure)
  - Exclusivity period for first-licensed interchangeable

Sources of Legal and Regulatory Requirements and FDA Policies

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Sources of Legal and Regulatory Requirements and 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.)
- Constitutional limits – "interstate commerce"

Regulations

- Binding source of law issued by FDA pursuant to statutory authority derived from, and in order to implement, the FDCA and PHSA (among other statutes)
  - "Regulation" and "rule" are often used interchangeably
  - FDA regulations are codified at Title 21 Code of Federal Regulations (C.F.R.)
- FDA's promulgation of a regulation requires "notice and comment" rulemaking, as specified by the Administrative Procedure Act (5 U.S.C. § 500 et seq.)
  - FDA is required to publish notice of proposed regulations in the Federal Register and to provide opportunity for public participation through written comments
  - Following public comment, FDA may issue a final rule, including information regarding the basis and purpose of the rule, generally not less than 30 days before the rule goes into effect
  - A final rule includes the codified text to be added to the C.F.R., FDA's explanation regarding the purpose of the rule, and any analysis of major issues or public comments

Federal Register Notices

- The Federal Register is the official journal of the federal government
  - Available in print or online at www.federalregister.gov

- Publication in the Federal Register is how FDA (and other agencies) give formal notice to the public of a variety of agency actions, including:
  - Proposed and final rules
  - Draft and final guidance documents
  - Forthcoming public meetings and workshops, including advisory committee meetings
  - Agency determinations, including determinations of patent extension periods and determinations of whether approved products were withdrawn from the market for reasons of safety or effectiveness
  - Submissions of proposed information collections to the Office of Management and Budget (OMB) for review

Preambles

- Preamble of a regulations refers to printed information that precedes text of regulation

- Preambles are not binding law but provide insight into FDA's position, including:
  - Explanation of FDA's purpose for proposing or issuing regulation
  - Explanation of FDA's view of the meaning and impact of regulation
  - Discussion of FDA's review and response to any public comments received

Advisory Opinions

- Advisory opinions represent FDA's formal position regarding a specific matter and—absent limited exceptions—must be adhered to by the Agency until amended or revoked (21 C.F.R. § 10.85)
  - FDA may issue advisory opinion in response to request from interested person (21 C.F.R. § 10.85(a))
  - Statements of policy or interpretation made in: (i) trade correspondence issued by FDA between 1938 and 1946; (ii) compliance policy guides codified in Compliance Policy Guides Manual; (iii) any portion of Federal Register notice, other than the text of proposed or final rules (e.g., preambles); or (iv) other documents specifically identified as advisory opinions (21 C.F.R. § 10.85(d))
  - FDA may not recommend legal action against person or product for action taken in conformity with advisory opinion (21 C.F.R. § 10.85(e))

Guidance Documents and Good Guidance Practices

- Guidance documents do not establish legally enforceable rights or responsibilities
  - Do not bind the public or FDA—otherwise, they would have to be promulgated via rulemaking
  - As a practical matter, guidance documents are widely followed
- Explain FDA's interpretation of, or policy regarding, statutory or regulatory issues
  - FDA issues more than 100 guidance documents per year
- FDA maintains policies and procedures for the development of guidance documents, known as Good Guidance Practices, or GGPs (21 C.F.R. § 10.115)

Compliance Policy Guides

- Compliance Policy Guides (CPGs) explain FDA policies on regulatory issues, and are practical in nature
  - Intended to advise both stakeholders and FDA's field inspection and compliance staff

Staff Manual Guides

- Staff Manual Guides (SMGs) describe FDA internal procedures
  - Do not create rights or bind the public or FDA

- Topics covered:
  - Organizations and functions
  - Delegations of authority
  - Administrative and program policies
  - Responsibilities and procedures

Compliance Programs

- Compliance programs are intended to guide FDA personnel on proper procedures for evaluating industry compliance with FDCA
  - e.g., inspection procedures

Enforcement Actions and Letters

- FDA may provide written notice of potential enforcement action:
  - Warning Letters
    - Issued when FDA finds significant violations of regulations
    - Identifies specific violation(s) at issue and provides timeframe for recipient response with plan for correction
    - Failure to take corrective may result in enforcement action
    - FDA maintains a public, searchable database of Warning Letters
  - Untitled Letters
    - Cite violations that do not meet the threshold of regulatory significance for Warning Letter
    - No public database, but may be made public

Enforcement Actions and Letters (cont.)

- Warning and Untitled Letters may provide insight into FDA's enforcement priorities and regulatory interpretations

- Enforcement actions may include, among other things, product seizures, mandatory recalls, and debarments

Citizen Petition Responses

- Citizen petitions are formal requests to FDA, asking the Agency to take or refrain from certain action
  - E.g., asking FDA to refuse to approve a generic drug or biosimilar application unless the follow-on product can meet a certain standard

- Citizen petition responses may provide insight into FDA's regulatory interpretations

Informal Statements and Advice

- Product sponsors and other stakeholders may solicit feedback from FDA on scientific and regulatory issues
  - May seek informal advice through e-mail, telephone, etc.
  - For more complex questions, sponsors may pursue formal meetings, which may include in-person meetings, teleconferences, written responses, or other methods of feedback
- Numerous FDA guidance documents on seeking and obtaining FDA feedback, including:
  - “Best Practices for Communication Between IND Sponsors and FDA During Drug Development”
  - “Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products”

Other Publications

- FDA and the Executive Branch make available general information, including:
  - Agency activities and basic information regarding regulatory frameworks
  - Planning initiatives
  - Budget information
  - Performance metrics and plans
  - User fee programs
  - Economic impact analyses

Standards

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International Conference on Harmonization

- Formed in 1990 and focused on international standardization of technical requirements for registration of pharmaceutical products
  - Makes recommendations intended to achieve consistency across regulatory agencies
  - Produces guidance documents related to technical drug development matters

- Certain ICH guidelines have been formally endorsed by FDA in guidance documents

Other Standards

- U.S. Pharmacopeia (USP)
  - Product quality standards
  - Embedded into FDCA definition of a drug
- International Organization for Standardization (ISO)
- Product- or industry-specific standards
  - Often used for medical devices

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
- Content requirements set forth in 21 C.F.R. § 10.30
- Posted to a public docket and subject to public comment
- Petitions are evaluated by FDA staff, who generate a formal response
  - FDA must respond to a citizen petition within 180 days of receipt or fewer, depending upon the statutory provision under which the petition was filed, but may provide a tentative response
- Following the review period, FDA may grant or deny the petition (in whole or in part), or dismiss it as moot
- Citizen petitions can be subject to antitrust scrutiny, and FDA can refer “sham” petitions to the FTC for enforcement action

Proposed Regulations and Guidance

- FDA generally issues regulations through “notice and comment” rulemaking
  - May issue Advance Notice of Proposed Rulemaking (ANPRM) soliciting information
  - Notice of Proposed Rulemaking (NPRM) in the Federal Register explains what FDA intends to do and the basis for proposal
  - NPRM establishes public comment period
  - Once FDA has reviewed public comments, the Agency decides whether to take further action (including ending rulemaking process, delaying proposed rule, or issuing new proposed or final rule)

- FDA also solicits public comments on draft guidance documents

Public Meetings

- FDA frequently hosts public meetings
  - Obtain public input, discuss proposed or existing regulations
  - Public workshops to provide information to stakeholders
  - Advisory committee meetings to discuss specific marketing applications or broader regulatory or scientific issues with independent experts

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 recommends that sponsors first attempt to resolve matter with responsible reviewing officials or division responsible
  - Sponsors may seek a formal meeting to discuss these matters and seek resolution

Formal Dispute Resolution

- Stakeholders can seek supervisory review up the chain of command (21 C.F.R. § 10.75)
  - Appeal is based on information in the administrative file
  - Sponsor may request scientific dispute be reviewed by appropriate advisory committee

- 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 PDUFA, GDUFA, and BsUFA, FDA attempts to respond within 30 calendar days

Regulatory Hearings

- FDA may decide, on its own initiative or following request, to offer opportunity for regulatory hearing to obtain information whenever Agency is considering regulatory action (or inaction), following procedures under 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
  - Notice will not delay or stay administrative action, unless determined by FDA to be in the public interest (21 C.F.R. § 16.22)

Regulatory Hearings (cont.)

- Generally public, unless FDA determines hearings should be closed in order to:
  - Protect privacy
  - Prevent disclosure of trade secret or other confidential information
  - Protect law enforcement records
- Generally presided over by FDA employee or administrative law judge
  - Presiding officer prepares written report of the hearing
  - Commissioner issued final written decision based on administrative record of the hearing
- After any final administrative action subject to a regulatory hearing under 21 C.F.R. Part 16, party may petition FDA for reconsideration or for stay of decision or action (21 C.F.R. § 16.119)

Judicial Review

- Administrative Procedure Act provides for federal judicial review of any “final” agency action

- FDA regulations acknowledge that affected persons may generally request judicial review of any Agency decision, provided that certain conditions are met (e.g., exhaustion of administrative remedies) (21 C.F.R. § 10.45)

- 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

Freedom of Information Act (FOIA)

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Obtaining and Protecting Information under FOIA

- 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

Obtaining and Protecting Information under FOIA

- FDA has discretion whether to disclose part or all of any FDA record that is otherwise exempt from mandatory disclosure, but may not disclose:
  - Information prohibited from public disclosure by statute
  - Trade secrets or commercial or financial information that is privileged and confidential
  - Personnel, medical, and similar files, disclosure of which would constitute a clearly unwarranted invasion of personal privacy
  - Information compiled for law enforcement purposes

Obtaining and Protecting Information under FOIA

- Procedure for preventing or challenging disclosure
  - Upon submission, stakeholders may 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

Questions?

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