FDA Compliance & Enforcement
General Principles

- Increased FDA portfolio requires increasingly strategic development and execution on enforcement policy;
- Institutional risk-based approach
- Focuses limited resources on:
  - Addressing public health threat
  - Vindicate important regulatory principle; or
  - Important deterrent value.
- Decentralized vs. Centralized Approach
- Congressional Interest in providing additional enforcement powers.
Jurisdictional Definitions

- Interstate Commerce
  - §301(a) prohibits introduction into interstate commerce any article that is adulterated or misbranded
  - §301(k) applies after even if the article becomes illegal after it is shipped in interstate commerce and “held for sale.”
    - Back door “new drug” charge
    - “held for sale” not limited to first sale; includes mere Bailee
    - Does not require conveyance of title to good

- Any component shipped in IC will render Act applicable
- Scienter Definition at §201(b)(b)
Principal FD&C Act Violations

- “Pre-Approval” Bars to Entry
- Adulteration (21 USC §351)
  - Consists in whole or in part of any filthy, putrid, or decomposed substance;
  - methods used in, or facilities or controls used for manufacture, processing, packing or holding are not in compliance with good manufacturing practice
  - Strength and purity profile differs from approved labeling
- Misbranding (21 USC §352)
  - Packaging or labeling may not be false or misleading in any particular
Principal FD&C Act Violations

- FD&A Act authorizes both civil and criminal remedies for the same violations.
  - Misdemeanor: first time criminal violation except where intent to defraud or mislead is present (FD&C Act §303(a)(1), 21 USC §333(a)(1))
  - Felonies: repeat offenses and those w/ requisite criminal intent (FD&C Act §303(a)(2), 21 USC §333(a)(2))
  - Civil penalties available for certain violations of the FD&C Act
  - Debarment persons convicted of certain crimes from future participation in the drug industry. (FD&C Act §306, 21 USC §335a)
Enforcement Tools

- Establishment Inspections
- Warning Letters and Other Regulatory Correspondence
- Recalls (FD&C Act §423, §518, §908(c), 21 USC §§350l, §360h, §387h(c))
- Publicity
- Administrative detention, product seizures, reconditioning / destruction
- Injunctions (including restitution, disgorgement of profits, and “liquidated damages”)
- Import inspections, detentions, and refusals, and re-export refusals (FD&C Act §801(r)m 21 USC §381(r))

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Enforcement Tools

- Product approval or license withdrawals, suspensions and “alter/reference” lists;
- Application integrity policy (deferral of review of applications)
- Civil Penalty Proceedings (FD&C Act §§303, 307, 21 USC 333, 335b)
- Debarment (FD&C Act, §306, 21 USC §335a)
- Misdemeanor Prosecutions
- Felony Prosecutions
- Government Wide Quality Assurance Program (GWQAP)
Inspections

- §703 of the FD&C Act (21 USC §373)
  - Without subpoena power, this provision gives FDA access to records held by a common carrier or records held in a facility that manufacturers, ships, or holds “food, drugs, devices, tobacco or cosmetics” as long that they are held for introduction into interstate commerce.

- §704 of the FD&C Act (21 USC §374)
  - Broader inspection power of plants that manufacture prescription drugs, nonprescription drugs for human use, restricted devices, tobacco products and infant formula.
  - FDASIA authorized FDA to obtain documents without being present for inspection; OCONUS parity.
Inspections

- **Colonnade-Biswell** exception to the warrant requirement for Fourth Amendment searches.
  - Exception provided for regulatory inspections of industries “long subject to close supervision and inspection”
  - Applied by the 8th Circuit Court of Appeals
- In concept, FDA can inspect an establishment either by warrant or by consent.
- Refusal to permit inspection after presentation of FDA credentials and Form 482 (Notice of Inspection) is a prohibited act under §301(f).
Inspections

- Where refused, FDA seeks a warrant this can lead to seizure, injunction, and a criminal prosecution.
- Can be part of action by FDA’s Office of Criminal Investigation (OCI).
- Inspections can be “directed” (specific products, documents) or “general” (complete facility).
- “reasonable times,” “within reasonable limits,” and in “reasonable manner.”
- §703 limited immunity provisions applies only to individual giving access to evidence (excludes it from criminal prosecution).
Inspections

- §704(b) of FD&C Act requires that Inspectional Observations (FDA Form 483 Facility)
  - Opinion of investigator as to possible violations
  - 15 days to respond to all observations
  - FDA will review response to determine whether to issue “Warning Letter”
  - 483 and responses are FOIA-able (though redacted)
  - District Office will create formal Establishment Inspection Report (EIR)
    - No action indicated (NAI)
    - Voluntary action indicated (VAI) [substantial issue but not regulatory action required]
    - Official Action indicated (OAI) [further administrative or judicial actions are required]
Warning Letters & Other Correspondence

- **Warning Letters**
  - Official Warning letters issued only for those violations of regulatory significance (i.e., that could lead to enforcement action if not promptly and adequately corrected)
  - vs. “Untitled Letters” (convey concern, but violations not serious enough – often called “notice of violation (NOV)” letters) vs. “Cyber Letters” (internet sellers; no response required)
  - WLs advice that enforcement action can take place without prior notice.
  - Request response (within 15 days)
Warning Letters & Other Correspondence

- Warning Letters (cont.)
  - Government-wide notice can impact other contracts
  - “hold” on preapproval applications or export approvals by FDA
  - Not considered “Final Agency Action” for purposes of Judicial Review but rather “informal and advisory”
  - Related press re: WLs create overwhelming pressure on the firm to comply
  - Close out Procedures depend on adequacy of the firm’s response.
Voluntary Recall

- FDA lacks the authority to force a company to recall a drug, rather their substantial influence results in voluntary recalls
  - Authority for mandatory recalls applies to: medical devices, tobacco products, foods (including dietary supplements and infant formula), and 351 biologics. Not drugs and cosmetics.
  - Class 1, 2 or 3 recalls, depending on the public health risk (21 CFR §7.41(b))
  - Depth, Effectiveness Checks, Termination
Voluntary Recall

- **Class I**
  - Most serious
  - “reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death” (21 CFR §7.3(m)(1))
  - Recall down to consumer level

- **Class II**
  - Product “may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote”
  - Retail level

- **Class III**
  - “not likely to cause adverse health consequences”
  - Wholesale level
Voluntary Recall

● Effectiveness Checks
  ● Range from A (100% of the consignees to be checked) to E (no effectiveness checks)
  ● FDA permits the use of personal visits, telephone calls, letters, etc.
  ● FDA relies on the firm to do this for the most part.

● Device Recalls
  ● §518 of the FD&C Act (as amended by the Safe Medical Devices Act of 1990) give recall authority for devices, they are usually voluntary.
  ● Informal hearing, notice, and recall order issued.
Publicity

- §705(a) and (b) of the FD&C Act gives FDA the duty to
  - publish “from time to time reports, summarizing all judgments, decrees, and court orders” and
  - disseminate “information regarding food, drugs, devices, or cosmetics in situations involving in the opinion [of FDA] imminent danger to health, or gross deception of the consumer.”
- Enforcement Report
- Consumer Report
- Public Health Advisories
- Press Releases
- Congressional Hearings
Seizure (21 USC §334(a)(1))

- Civil remedy that provides for judicial condemnation of the goods at issue and either (i) destruction of the goods or (ii) an FDA-supervised reconditioning procedure.
- FDA files Complaint in District Court listing allegations regarding product and whether adulterated or misbranded
- This is an in rem (against property) action
- Court issues order of attachment authorizing the U.S. Marshall to physical execute the order by going to the location and affixing the order to the property.
Seizure (21 USC §334(a)(1))

- Attempts to hide the adulterated or misbranded product is obstruction of justice
- Government must provide claimants notice of need to file claim in court for the property.
- Multiple Seizures (multiple actions in different jurisdictions simultaneously) available under §304 of the FD&C Act
- Mass Seizure (e.g., broad adulteration action extends to whole facility) (21 USC 342(a)(4), 351(a)(2)(B)).
Injunction (21 USC §332)

- Civil action against the Company or individuals
- Utilized to enjoin conduct where there is a likelihood that violations will continue or recur.
- Restrained and enjoined from additional manufacture and introduction into interstate commerce
  - TRO
  - Disposition: Trial, Summary Judgment, Consent Decree
- Can range from no introduction of new products to complete shut-down of a manufacturing facility
- Employed where immediate action required.
Injunction (21 USC §332)

- Consent decree elements may include shut down of facilities, remedial action and re-audit by FDA and other equitable remedies.
  - Considerable controversy over disgorgement of profits, yet, Courts have upheld FDA’s ability to see this remedy
  - Liquidated damage remedy also debated.
Administrative Powers

- Secretary of HHS may immediately suspend the approval of an NDA upon a finding of an imminent hazard to the public health (21 USC §355(e))
- Withdrawal of approval can be based on cGMP violations (21 CFR §210)
- Revocation of biologic product and establishment licenses for various types of non-compliance (21 CFR §601.5)
- During investigational phase, FDA may disqualify investigators, IRBs, laboratories, sponsors and may terminate IND or IDEs
Administrative Powers

- Ban devices where there is an unreasonable risk of illness or injury (21 USC §360f)
- Application Integrity Policy (AIP)
  - Titled “Fraud, Untrue Statements of Material Facts, Bribery and Illegal Gratuities; Final Policy” (1991)
  - Approach to review applications affected by wrongful acts that raise significant questions about data reliability
  - FDA an refuse to approve an application that contains unreliable data and may withdrawal approval if the application was approved
  - If evidence of fraud is widespread, FDA can apply policy to all of company’s future or pending submissions.
Administrative Powers

- Debarment of corporations from the FDA approval process (21 USC §335a(a)(1))
- Debarment of individuals from the pharmaceutical industry (21 USC §335a(c)(1)(B))
- Withdrawal and suspension of product approvals (21 USC 335a(g)(1))
- Whistleblower awards up to $250,000 (21 USC §333(b)(5))
Criminal Powers

- FDA is a law enforcement entity and the fear of criminal prosecution remains a significant deterrent;
- FDA decides to recommend to DOJ criminal prosecution in cases where:
  - Gross violations that evidence mgmt.’s disregard for unsafe conditions;
  - Obvious and continuous violations where mgmt. has not exercised normal care
  - Life-threatening violations or where injuries have occurred
  - Deliberate attempts to circumvent the law.
Criminal Powers

- FDA will request DOJ obtain information or an indictment, depending on whether a misdemeanor or felony charge is sought.
- DOJ’s Office of Consumer Protection Branch then takes over the case as FDA’s representative (Assistant U.S. Attorney prosecutes).
Criminal Penalties

Criminal and Civil Penalties Available

- Violations of §301 FD&C Act (Prohibited Acts) could result in imprisonment for 1 year and a $1,000 fine or both for first offense (21 USC §333(a)(1)), 3 years and $10,000 for subsequent offense (21 USC §333(a)(2))
- Violations of Prescription Drug Marketing Act Provisions incurs a penalty of 10 years imprisonment and fines of not more than $250,000. (21 USC §333(b)(1))
- Intentionally adulterating a drug that has a reasonable probability of causing serious harm incurs 20 years imprisonment or $1 Million or both. (21 USC §333(b)(7))
- Importation violations escalate from $50,000 to $1 million dollars;
Criminal Penalties

- Criminal and Civil Penalties Available
  - Any criminal charge under 21 USC can also be brought under 18 USC, for example, conspiracy, etc. Maximum penalties and Federal sentencing guidelines would apply.
  - (civil) Increased device penalties (21 USC §331(f) allows for $15,000 for each violation, aggregate at $1 Million)
  - (civil) $1 Million for violation of post-marketing requirements, up to $10 million for each subsequent.
  - (civil) False and Misleading DTC Advertising, Failure to submit clinical trial certifications, etc.
  - Injunctive remedy to extract high-dollar civil money penalties
Criminal Penalties

- The “Park” Doctrine
    - FDA names individual corporate officers or employees in all its criminal referrals.
    - In Park, Supreme Court applies strict liability criminal misdemeanor standard on responsible corporate officials.
    - Even without direct knowledge of violation, liability applies where there is “responsibility and authority either to prevent in the first instance, or promptly correct, the violation”
  - FDA’s Regulatory Procedures Manual Explains Use of Park Doctrine
    - “consider the individual’s position in the company and relationship to the violation, and whether the official has the authority to correct or prevent the violation”
Criminal Penalties

The Role of Guaranties

- 21 USC §333(c)(2) provide “safe harbor” from criminal liability where guaranty involved:
  - guaranty received by a corporation or individual stating that the article delivered by the guarantor is not adulterated or misbranded within the meaning of the FD&C Act and (as applicable) they are not unapproved food additives, color additives, new drugs, or Class III devices subject to pre-approval.
  - Limited to specific shipment OR general/continuing.
  - Expires when shipped or delivered
  - Subsequent adulteration still criminally actionable.
  - Safe harbor does not preclude seizure, injunction or recall
Enforcement Discretion

- §305 Hearing (21 USC §335)
  - For criminal violations, FDA may elect to give notice of the violation and an opportunity to be heard to the company. Formal process before charges filed.
  - Strategic considerations for FDA (destruction of evidence) vs. company (disclosure = additional evidence)

- Risk-based Enforcement Discretion
  - No statutory provision dictating how FDA is to utilize its limited resources to remedy all the violations that are reported to or discovered by the Agency.
  - Courts generally will not review decisions not to pursue