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Violations and Enforcement

Tiffany M. Humphries, Senior Associate | Wednesday, November 10, 2021

Agenda

1. The Interstate Commerce Element
2. Prohibited Acts
3. Enforcement Tools and Procedures
4. FDA Commissioner’s Enforcement Initiatives

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The Interstate Commerce Element

Interstate Commerce

FDA's jurisdiction

- The introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded [is a prohibited act]. 21 U.S.C. 331(a).

- The term "interstate commerce" means (1) commerce between any State or Territory and any place outside thereof, and (2) commerce within the District of Columbia or within any other Territory not organized with a legislative body. 21 U.S.C. 321(b).

  - *Presumption of Interstate Commerce Jurisdiction* – "In any action to enforce the requirements of this chapter respecting a device, tobacco product, food, drug, or cosmetic the connection with interstate commerce required for jurisdiction in such action shall be presumed to exist." 21 U.S.C. § 379a.

Interstate Commerce

FDA's jurisdiction

- The Federal Food, Drug, and Cosmetic Act ("FDCA") gives FDA broad authority to regulate the marketing or distribution of drugs, biologics, medical devices, food, cosmetics and dietary supplements in **interstate commerce** (*e.g.*, mail, wire, and other mechanisms of interstate commerce).
- The FDCA also gives FDA broad authority to regulate the content of product **labeling** as well as **advertising** for drugs, biologics, restricted devices (*e.g.*, Rx devices) and tobacco products.

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Prohibited Acts

21 U.S.C. 331

- Section 301 of the FDCA lists over 40 "**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)
  - Most common violation: "introduction or delivery for introduction into interstate commerce of any . . . [drug] that is **adulterated** or **misbranded**"

21 U.S.C. 331

- 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.)

Adulteration and Misbranding

- The FDCA prohibits distribution of **adulterated** or **misbranded** products in interstate commerce
  - *See* 21 U.S.C. §§ 331(a)-(c), (g), (k) ("prohibited acts" involving adulterated and misbranded product)
- Adulteration can result from:
  - being prepared, packed, or held under insanitary conditions
  - not manufactured in accordance with CGMP requirements
- Misbranding can result from:
  - "False or misleading" product labeling or advertising (e.g., off-label promotion)
  - Absence of required information in labeling or advertising
  - Violations of various requirements (e.g., registration, adverse event reporting, etc.)

Misbranding and Adulteration by Product

Product	FDCA Section
Food	402 - Adulteration
Food	403 - Misbranding
Infant Formula	412 - Adulteration
Dietary Supplements	413 - Adulteration
Dietary Supplements	403(s) - Misbranding
Drugs & Devices	501 - Adulteration
Drugs & Devices	502 - Misbranding
Cosmetics	601 - Adulteration
Cosmetics	602 - Misbranding

Who is held liable for prohibited acts?

- **Owners and operators**
  - Companies or facilities that make, distribute, or market FDA-regulated products

- **Individuals and "responsible corporate officers"**
  - An executive who stands in "responsible relation" to public danger
  - Can be anyone with authority to prevent or detect and correct violations
    - Highest ranking corporate officer (*e.g.*, president or CEO)
    - Executive with direct authority to implement corrective actions (*e.g.*, director of regulatory affairs or director of corporate compliance)
    - Could also include Legal staff

- "**Applicants**" or "**sponsors**"
  - Who conduct or oversee clinical trials (*i.e.*, research on humans) or submit research or marketing applications to FDA

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Enforcement Tools and Procedures

FDA's Enforcement Tools

- **Advisory Tools** (FDA executes on its own)
  - FDA Form – 483 (Notice of Inspectional Observations)
  - Untitled Letter
  - Warning Letter
  - Adverse Publicity
- **Administrative Tools** (FDA executes on its own)
  - Import detentions or import refusals
  - Mandatory Recalls
  - Clinical Holds
  - Application Integrity Process
  - Investigator Disqualification or Restrictions (NDIPOE)
  - Civil Money Penalties
  - Withdrawal of Marketing Approval
- **Judicial Tools** (FDA must go to court, through DOJ)
  - Seizure
  - Injunction (including disgorgement)
  - Criminal Prosecution (including restitution)
  - Consent Decrees and Settlements

Warning Letters and Untitled Letters

Advisory communications intended to give the recipient:

- Notice of significant regulatory violations
- An opportunity to take voluntary and prompt corrective action before the agency initiates an enforcement action (e.g., recall, seizure, injunction, etc.)
- Include an explanation of why corrective actions in response to FDA Form 483 notice are or were inadequate
- Does not commit FDA to taking enforcement action
- Not a prerequisite to taking enforcement action (e.g., if violation reflects a history of repeated or continual conduct, is intentional or flagrant, presents a reasonable possibility of injury or death)

Warning Letters are often reported by major news outlets and trade press, and may lead to significant adverse publicity.

Adverse Publicity

- Section 705 of the FDCA allows FDA to disseminate information "in situations involving, in the opinion of [FDA], imminent danger to health or gross deception of the consumer"
  - Safety alerts (e.g. MedWatch and the Counterfeit Alert Network); press releases; and recall notices
  - FDA is increasingly using Adverse Publicity in lieu of, or in conjunction with other enforcement mechanisms
    - e.g., FDA already has 25 drug-related alerts on its website for 2021

- FDA routinely issues press releases upon filing of enforcement actions
  - Announcements may affect stock prices
  - May adversely affect reputation of company and individual officers

Voluntary Recalls

- A voluntary action by a company at any time to remove a defective drug product from the market (i.e., misbranded or adulterated)
- Public notification is generally issued when a product that has been widely distributed or poses a serious health hazard is recalled
- If a company does not issue public notification, FDA may do so if the agency determines it is necessary to protect users
- Recalls are posted weekly on FDA's website in enforcement report by classification
  - Class I: could cause serious health problems or death
  - Class II: may cause temporary health problem or slight serious threat
  - Class III: violative but unlikely to cause adverse health threat

Civil Money Penalties

- The FDCA contains specific statutory provisions that permit FDA to impose CMPs through an administrative process
  - CMPs may be sought separately from, or in connection with, another civil or criminal action under the FDCA
  - Maximum penalty for each violation depends on the authorizing statute and is adjusted periodically for inflation
- Procedures established by Regulation, 21 C.F.R. Part 17
  - FDA's Office of Chief Counsel (OCC) initiates proceedings with a Complaint filed with FDA's Division of Dockets Management
  - Plaintiff (called "Complainant") is the FDA Center with principal jurisdiction over the product at issue
  - Defendants (called "Respondents") are given notice and opportunity for hearing before an Administrative Law Judge (ALJ)
  - After answer has been filed, the Center must serve notice of hearing on Respondent
  - ALJ will provide guidelines for the proceeding (rules for filing, communication between parties, etc.)

Seizures

- Section 304(a) authorizes the FDCA authorizes the U.S. government to seize violative goods. 21 U.S.C. § 342(a)
  - Actions governed by the Supplemental Rules for Certain Admiralty and Maritime Claims (Supplemental Rules); action is against the goods or articles themselves
  - Seizure initiated when DOJ files a Complaint for Forfeiture and obtaining a warrant for arrest, directing the United States Marshal to seize (take possession or place in constructive custody of the court) the article.
  - The government asks the court to “condemn” the seized goods and declare forfeiture for violation of the law by the article itself.
  - Any interested party, owner, or agent may appear to claim the article by filing a verified claim stating the nature of his/her interest in the article.

Injunctions

- Section 302 of the FDCA authorizes injunctions to restrain most violations of Section 301
  - Action against an individual or company or both
  - Evidence of actual injury or harm not required

- Two types of Injunction
  - Prohibitive
    - Defendant may not engage in designated activity “unless or until” FDA finds that defendant has come into compliance
  - Mandatory
    - Defendant may continue to engage in designated activity, but must take specific actions, pursuant to specific timetable, or be subject to penalties or other sanctions

- Criteria for Recommendation
  - Evidence of recent violations with prior history of same
  - Cessation of operations is needed to halt the flow of violative products in interstate commerce
  - Health hazard or gross consumer deception requiring immediate action
  - Failure to correct pre-existing violations
  - Significant amounts of violative products owned by the same person or company in several different locations

Criminal Prosecution

- Section 303(a) of the FDCA imposes criminal sanctions against persons who commit a prohibited act or cause such acts to be committed
  - Felony if done with intent to defraud or mislead, or a second offense without intent
  - Misdemeanor without a showing of intent

- Typically recommended for
  - Manufacturing and sale of counterfeit and unapproved drugs or
  - Illicit prescription drug diversion, substitution or tampering crimes
  - Fraudulent health treatments, Fraud involving NDAs, PMAs, or clinical investigations
  - Continuous, repeated, gross, flagrant, or intentional FDCA violations
  - Evidence of actual harm or injury to the public as a result of FDCA violations

- Consequences
  - **Strict misdemeanor criminal liability** for corporations and individuals that commit enumerated prohibited acts
  - **Strict felony liability** for recidivists
  - Fines, penalties, restitution, disgorgement, forfeiture of assets or imprisonment
  - Courts may order restitution for violations of Title 18 of the U.S. Code. See 18 U.S.C. §§ 3663 and 3663A

Debarment

- An enforcement proceeding that prohibits an individual from working in any capacity in the drug industry
- In the drugs context, FDA **must** debar an individual convicted of a felony under federal law related to the development or approval of a drug, or the regulation of a drug (usually permanent)
- In the drugs context, FDA **may** debar an individuals convicted of a federal misdemeanor or state felony (or conspiracy to commit a misdemeanor or felony, or aiding another to do so) for a period of several years
- So far, in 2021, there have been 8 drug-related debarments of individuals

Debarment

Example of facts for a permissive debarment order for a 5-year period, effective 3/26/21

The debarred individual was convicted of a felony, to which she pleaded guilty, for conduct in or about June 2016 and continuing to on or about June 21, 2018. The individual operated a blog under the name “the Macrobiotic Stoner” and a fake jewelry business under the name “Morocco International Inc.” She used both entities to sell unapproved and misbranded prescription drugs to consumers in the United States and around the world and to process payments for those drugs. Throughout the course of this conspiracy the individual did not possess a valid wholesale drug distribution license, pharmacy license, or a license to prescribe prescription drugs. She was also not registered under section 510 of the FD&C Act (21 U.S.C. 360) as a person who owns or operates an establishment engaged in the manufacture, preparation, propagation, compounding, or processing of a drug.

Further, the individual imported foreign-sourced prescription drugs in wholesale quantities from India into the United States. The imported drugs contained U.S. Customs Declaration Forms falsely stating that the contents were “personal supply medication” and did not contain any dangerous articles or articles prohibited by postal or customs regulations. The drugs imported were, in fact, foreign versions of mifepristone and misoprostol.

Application Integrity Policy (AIP)

- Invoked when sponsor has committed a “wrongful act” or made an “untrue statement of material fact”
  - A wrongful act is any act that may subvert the integrity of the review process
  - An “untrue statement of material fact” is a false statement, misstatement, or omission of fact
  - A determination that an untrue statement is material is necessary for purposes of invoking the AIP

- Criteria for Invoking
  - Pattern or Practice of Wrongful Conduct
  - Significant Question of Data Reliability
  - System-wide Failures
  - Decision made by Center Director, the Division of Bioresearch Monitoring with input from others (e.g., compliance, chief counsel, etc.)

Imports: Detention/Refusal

- Section 801(a) authorizes FDA to conduct import examinations, inspections, label/records reviews, and physical sampling and testing.
- FDA may **detain** where there is evidence pointing to a violation
  - brief examinations are sufficient
  - examination is not always necessary, (e.g., where a violation was found in a previous shipment of the product from the same firm)
- FDA may **refuse** an entry if it "appears from the examination" that
  - Imports were "manufactured, processed, or packed under insanitary conditions" or, for devices, the manufacture, packing, storage or installation of the device are not incompliance with Section 520(f); or
  - Imports are "forbidden or restricted in sale in country in which it was produced/from which it was exported, or
  - Imports are adulterated, misbranded, or in violation of section 505 or prohibited entry/introduction into interstate commerce under section 301(ll)
- If shipment is refused, shipment is….
  - Destroyed unless exported within 90 days of refusal.
    - If owner has possession of goods (after having posed sufficient bond), must redeliver goods pursuant to the Bond agreement. Customs may collect liquidated damages if goods are not redelivered.

Import Alerts

- Inform FDA's field staff and the public that the agency has enough evidence to allow for Detention Without Physical Examination (DWPE) of products that appear to be in violation of the FDA's laws and regulations
- DWPE allows the agency to detain a product without physically examining it at the time of entry.
- Violations could be related to the product, manufacturer, shipper and/or other information

Types of Import Alerts (from fda.gov)

Category of Import Alert	Instructions	Violation Example
Country- or area-wide	The FDA may detain without physical examination certain products offered for entry from the specified country or area.	EXAMPLE: Import Alert #12-03 “Detention without Physical Examination of Imported Soft Cheese and Soft Ripened Cheese from France.”
Manufacturer/Product Specific	The FDA may detain without physical examination certain products from specific manufacturers.	EXAMPLE: Import Alert #89-16 “Detention Without Physical Examination of Products from Medical Device Firms Refusing FDA Foreign Establishment Inspection.” EXAMPLE: Import Alert #99-37 "Detention Without Physical Examination of Low-acid Canned Foods and Acidified Foods Without Filed Scheduled Processes.
Shipper	The FDA may detain without physical examination certain products from shippers.	EXAMPLE: Import Alert #16-105 "Detention Without Physical Examination of Seafood and Seafood Products from Specific Manufacturers/Shippers Due to Decomposition and/or Histamines." A specific shipper was found to have caused the violation.
Country/World Wide Alert	The FDA may detain without physical examination certain products from all countries outside of U.S.	EXAMPLE: Import Alert #16-20 “"Detention Without Physical Examination of Puffer Fish." There is a high fatality rate among those who ingest tetrodotoxin, a toxin found in puffer fish. The toxin cannot be destroyed by cooking or freezing. Therefore, the importation of puffer fish products is restricted. There have been several serious illnesses which have occurred due to puffer fish that were illegally imported into the U.S.

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FDA Commissioner's Enforcement Initiatives

FDA Commissioner?

President Biden still has not named an FDA Commissioner…

- Current Acting Commissioner is Dr. Janet Woodcock, who was named in January.
- She has served as the director of the Center for Drug Evaluation and Research, the FDA Center that approves new drugs, twice.
- She has also served as the acting commissioner previously.
- Rumors that Dr. Robert Califf may be appointed.
- Permanent Commissioner must be nominated by 11/15.

“As we heard from one individual in long term recovery, ‘The opposite of addiction is connection, not isolation.’ Indeed, the increased isolation of the past year may be a contributing factor in the rise in the number of overdose deaths over this period, a complication of the documented psychological distress caused by the imposed isolation during the COVID-19 pandemic… According to the Centers for Disease Control and Prevention’s provisional data, there were a reported 85,516 drug overdose deaths in the 12-month period ending in August 2020 – the highest number of overdose deaths ever recorded in a 12-month period.”

Dr. Janet Woodcock, 2021 Rx Drug Abuse and Heroin Summit, 4/8/21

FDA Priorities

2021 FDA Actions on the Opioid Abuse Crisis

i. FDA provided an update on its efforts to locate and remove websites that illegally offer unapproved opioids. The FDA claimed the 120-day pilot program successfully removed 30 of such websites.

ii. FDA provided an update on the pilot program with the National Telecommunications and Information Administration (NTIA) and three domain name registries to help reduce the availability of unapproved opioids illegally offered for sale online. Specifically, on February 16, the FDA issued a warning letter to AcelRX Pharmaceuticals Inc. for false and misleading promotion of Dsuvia - a potent opioid analgesic.

iii. On March 1, the FDA approved Hydrocodone bitartrate - the first FDA-approved generic opioid with an abuse-deterrent formulation. This generic opioid contains properties that reduce abuse of the drug when taken; although, it does not prevent abuse.

iv. On March 24, the FDA issued Introduction to FDA's Opioid Systems Model - a white paper that discusses the FDA's opioid systems modeling effort and the areas for further policy analysis and work.

Trump v. Biden Administration Priorities

- The Biden Administration released a $131.7 billion budget request for HHS that includes increased funding to combat the coronavirus pandemic and opioid crisis.
- $10.7 billion would be directed towards the opioid crisis. This is nearly $4 billion more than 2021's budgeted amount to combat the crisis.
  - About 2/3 of drug overdoses involve opioids and overdoses have continued to increase during the pandemic.

Trump v. Biden Administration Priorities

- On January 27, 2021, the Biden Administration reversed Trump Administration guidelines that relaxed requirements for prescribing buprenorphine - an opioid addiction medication.
- The Trump Administration guidelines removed a requirement that physicians take an 8-hour training course to obtain a waiver from the DEA to prescribe the medication.

Poll: Is CBD Legal?

YES

FDA Priorities

Enforcement Against CBD Products

- It is prohibited to add add CBD as an ingredient to food products or dietary supplements.
- The Farm Bill legalized the production of industrial hemp and products derived from hemp, but it did not legalize all uses of and products containing hemp derivatives (including CBD).
- FDA's CBD-related enforcement has focused on disease or health claims as evidence of the products' intended use. Intended use can be determined by evaluating claims in the labeling, advertising, or promotion; and consumer perceptions.
- Products, other than foods, that are intended to diagnose, cure, mitigate, treat or prevent a disease, or affect the structure or function of the human body are drugs.

FDA Priorities

Enforcement Against CBD Products

Warning letter to Honest Globe, Inc., issued March 15, 2021

"Currently, a nonprescription drug product containing CBD cannot be legally marketed without an approved new drug application, regardless of whether the CBD is represented on the labeling as an active ingredient or an inactive ingredient. To date, no CBD-containing drug has met applicable FDA requirements to be legally marketed for nonprescription use. As explained below, nonprescription drug products that include CBD as an active ingredient are not generally recognized as safe and effective (GRASE) and are new drugs which require an approved application to be legally marketed."

FDA Priorities

Enforcement Against CBD Products

Warning letter to Honest Globe, Inc., issued March 15, 2021

"[A]n inactive ingredient should not exert pharmacological effects and must be safe when used at the intended dosage. CBD, however, has known pharmacological activity with demonstrated risks. It is unknown whether the levels of CBD used in your … products have pharmacological activity or pose any concern for safety events."

"Accordingly, CBD cannot be considered a safe and suitable inactive ingredient as required under 21 CFR 330.1(e). Consequently, if CBD is intended to be an inactive ingredient in your … product, that product would not meet the general requirements for nonprescription drugs needed for legal marketing under sections 505G(a)(1) or (2)."

FDA Priorities

Enforcement Against CBD Products

Warning Letter to Biolyte Laboratories, LLC, Issued March 18, 2021

“[E]ven if CBD could be considered an inactive ingredient in a nonprescription drug product, that product would still need an approved new drug application to be legally marketed because the product would not be eligible for marketing under section 505G of the FD&C Act. In particular, such product would not meet the conditions under section 505G(a)(1) or (2), insofar as it would not conform with the general requirement in 21 CFR 330.1(e) that inactive ingredients must be safe and suitable. A suitable inactive ingredient generally provides a beneficial formulation function, such as a tablet binder or preservative, or improves product delivery (e.g., enhances absorption or controls release of the drug substance). CBD has no known functional role as an inactive ingredient in a finished drug product. Additionally, an inactive ingredient should not exert pharmacological effects and must be safe when used at the intended dosage. CBD, however, has known pharmacological activity with demonstrated risks.”

Questions

Baker McKenzie.

bakermckenzie.com