Post-Approval Drug Issues

Introduction to Drug Law and Regulation

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Agenda

- Establishment Registration and Drug Listing
- Adverse Drug Experience (ADE) Reports
- Other Postmarketing Reports
- FDA Drug Safety Activities
- Post-Approval Changes and Supplements NDAs (sNDAs) and ANDAs
- Grounds for Withdrawal of Approval
- Medicare, Medicaid and Reimbursement Issues
- Prescription Drug Marketing Act (PDMA)/Pedigrees/Authentication
- “Real World” Applications

Establishment Registration and Drug Listing

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Registration Requirements

- Establishment Registration
  - Manufacturers, repackagers, relabelers, CMOs, API manufacturers
  - Domestic and foreign
  - Must register within 5 days
  - Annual renewal
  - User fees (PDUFA/GDUFA/BSUFA)
  - 21 C.F.R. § 207.17; 207.21; 207.29
- Drug Listing Process
  - Initial registration
  - June/December Updates
  - 21 C.F.R. § 207.41; 207.49; 207.53; and 207.54; 207.57

Adverse Drug Experience (ADE) Reports

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What is an ADE?

Definition: Any adverse event ***associated with*** the use of a drug in humans, whether or not considered drug related, including the following:

- An adverse event occurring in the course of the use of a drug product in professional practice;
- An adverse event occurring from drug overdose whether accidental or intentional;
- An adverse event occurring from drug abuse;
- An adverse event occurring from drug withdrawal; and
- Any failure of expected pharmacological action. 21 C.F.R. § 314.80(a); 310.305.

Review Requirement

Applicant must “promptly review” all ADE information “from any source, foreign or domestic, including information derived from commercial marketing experience, postmarketing clinical investigations, postmarketing epidemiological/surveillance studies, reports in the scientific literature, and unpublished scientific papers.” 21 C.F.R. § 314.80(b).

Question

- When must an ADE be reported to FDA?
  - Rare
  - Serious
  - Unexpected
  - Common

Reporting Requirements

- 15-day Alert Reports
  - ADEs that are both serious and unexpected must be reported ASAP but no later than 15 calendar days from initial receipt of information and promptly investigate. 21 C.F.R. § 314.80(c)(1).
  - 15-day Follow-up Alert Reports
- Periodic ADE Reports
  - ADEs that are not serious or are expected must be reported quarterly for the first 3 years after approval and then annually. 21 C.F.R. § 314.80(c)(2).

Serious ADE

- Any adverse drug experience occurring at any dose that results in any of the following outcomes:
  - Death
  - A life-threatening adverse drug experience
  - Inpatient hospitalization or prolongation of existing hospitalization
  - A persistent or significant disability/incapacity, or
  - A congenital anomaly/birth defect. 21 C.F.R. § 314.80(a).

Unexpected ADE

- Any adverse drug experience that is not listed in the current labeling for the drug product.
  - An adverse experience that has not been previously observed. 21 C.F.R. § 314.80(a).

Periodic Report Criteria

- Descriptive information
  - Summary and analysis of the information in the report
  - An analysis of the 15-day Alert reports submitted during the reporting interval
- Individual Case Safety Reports (ICSR)
- FDA Adverse Event Reporting System (FAERS) Public Dashboard allows the general public to search for information related to human adverse events reported to the FDA by the pharmaceutical industry, healthcare providers and consumers.

Individual Case Safety Reports (ICSR)

- Minimum Data Elements
  - Identifiable patient
  - Identifiable reporter
  - Reaction or event
  - Suspect drug product
- Submitted electronically
- For specific format, see Specifications for Preparing and Submitting Electronic ICSRs and ICSR Attachments Technical Specifications Document- February 2018

Submission and Recordkeeping

- FAERS database - must be submitted in electronic format. 21 C.F.R. § 314.80(g).
- Maintain all ADE information for 10 years. 21 C.F.R. § 314.80(g).
  - Failing to report or maintain records may result in withdrawal of approval. 21 C.F.R. § 314.80(k).

Other Postmarketing Reports

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NDA – Field Alert Report (FAR)

- Applicant must report to FDA District Office within 3 working days of receipt:
  - Incident that causes the drug product or its labeling to be mistaken for, or applied to, another article.
  - Bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product.
  - Any failure of one or more distributed batches of the drug product to meet the specification established for it in the application.

    21 C.F.R. § 314.81(b)(1)
- Form FDA 3331a to submit FARs for CDER or CBER regulated drug products that are approved under an NDA or ANDA.
  - Electronic preferred

Annual Report

- Applicant must report within 60 days of “anniversary date”:
  - Summary of new information
  - Distribution data
  - Authorized generic drugs
  - Labeling
  - CMC changes
  - Non-clinical studies
  - Clinical data
  - Status reports of postmarketing studies. 21 C.F.R. § 314.81(b)(2).

Advertisements and Promotional Labeling

Form 2253 – “mailing pieces and any other labeling or advertising…at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product.” 21 C.F.R. § 314.81(b)(3)(i).

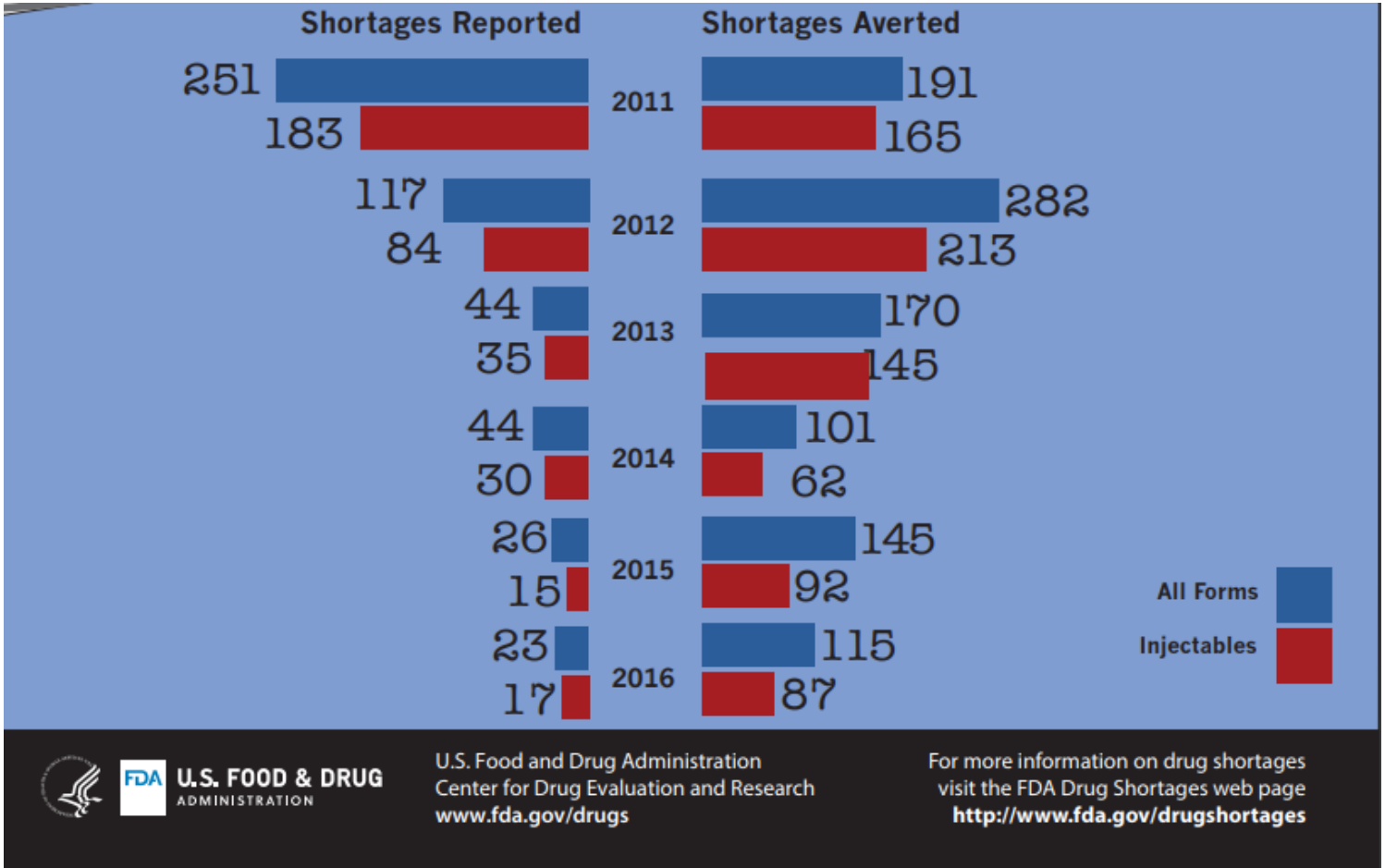
Special Reports

FDA may require that the applicant submit one of the aforementioned reports at a different time then stated in the regulations. 21 C.F.R. § 314.81(b)(3)(ii).

Notification Discontinuation or Interruption

Applicant must notify in writing of “permanent discontinuance of manufacture of the drug product or an interruption in manufacturing of the drug product that is likely to lead to a meaningful disruption in supply of that drug.” 21 C.F.R. § 314.81(b)(3)(iii).

Notification of Shortage



FDA Drug Safety Activities

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Risk Evaluation and Mitigation Strategy (REMS)

- Post-approval safety strategies to manage a known or potentially serious risk associated with a medicine.
- Can be required by FDA, but is not required for all drugs.
- “REMS are designed to help reduce the occurrence and/or severity of certain serious risks, by informing and/or supporting the execution of the safe use conditions described in the medication's FDA-approved prescribing information.”
- Example: Zyprexa Relprevv REMS

Phase IV Studies

- Postmarketing studies or clinical trials may be required by FDA to gather additional information about drug safety, efficacy, or use.

Post-Approval Changes and Supplements NDAs (sNDAs) and ANDAs

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Changes to Approved NDA

- Notification is required for “each change in each condition established in an approved NDA beyond the variations already provided for in the NDA.” 21 C.F.R. § 314.70(a).
  - Assess the effects of the change prior to distributing the product with the change.

Major Changes

- Any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a ***substantial potential*** to have an adverse effect on the:
  - Identity
  - Strength
  - Quality
  - Purity
  - Potency of the drug product
- Requires a supplement submission and prior approval from FDA. 21 C.F.R. § 314.70(b).

Moderate Changes

- Any change in the drug substance, drug product, production process, quality controls, equipment, or facilities that has a ***moderate potential*** to have an adverse effect on the:
  - Identity
  - Strength
  - Quality
  - Purity
  - Potency of the drug product
- Requires a supplemental submission at least 30 days prior to distribution. 21 C.F.R. § 314.70(c).

Minor Changes

- Changes in the drug substance, drug product, production process, quality controls, equipment, or facilities that have a ***minimal potential*** to have an adverse effect on the:
  - Identity
  - Strength
  - Quality
  - Purity
  - Potency of the drug product
- Must be documented in the next annual report. 21 C.F.R. § 314.70(d).

Grounds for Withdrawal of Approval

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Question

- What are ground for withdrawing approval?
  - Refuse FDA inspection
  - New information shows that the drug is not safe
  - Failure to file required reports
  - Drastic price increase

Section 505(e)

- **Mandatory withdrawal – "shall"**
  - Clinical or other experience, tests, or other scientific data show that such drug is unsafe
  - New evidence of clinical experience or tests by new methods shows that such drug is not shown to be safe
  - New information shows that there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof
  - Patent information was not properly filed
  - The application contains any untrue statement of a material fact if there is an imminent hazard to the public health

Section 505(e)

- **Discretionary withdrawal – “may”**
  - The applicant has failed to establish a system for maintaining required records, or has repeatedly or deliberately failed to maintain such records or to make required reports or to comply with the notice requirements
  - New information related to the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to assure and preserve its identity, strength, quality, and purity and were not made adequate within a reasonable time after receipt of written notice from the Secretary
  - The labeling of the drug, based on a fair evaluation of all material facts, is false or misleading in any particular, and was not corrected within a reasonable time after receipt of written notice from the Secretary

Additional Cause for Withdrawal

- FDA finds that applicant fails to maintain required records
- Methods and controls used in manufacturing, processing and packing is inadequate
- Labeling is false or misleading and not corrected within a reasonable time
- Studies were not conducted in compliance with FDA requirements
- No longer marketed
- FDA can request withdrawal if it believes there is “potential problem associated with a drug is sufficiently serious that the drug should be removed from the market and may ask the applicant to waive the opportunity for hearing”. 21 C.F.R. § 314.150.

Other Potential Reasons for Withdrawal

- Citizen petition
- “Imminent hazard” to public health
- Advisory Committee recommendation
- “Administrative Reconsideration”

Medicare, Medicaid and Reimbursement Issues

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Reimbursement and Coverage

- FDA is not responsible for setting reimbursement rates or insurance coverage for drug products.
- Pricing issues are not within the purview of the FDA
- FDA generally does not consider price and its recent statements related to drug compounding seem to follow along, but it has used enforcement discretion in the past (e.g., Makena approval).

Reimbursement and Coverage

- Just because a drug gets FDA-approval does not mean it will be reimbursed by payers
- There is often a lag between FDA-approval and a coverage determination
- Payer coverage is a separate process
  - Federal payers
  - Commercial insurance

Prescription Drug Marketing Act (PDMA)/Pedigrees/Authentication

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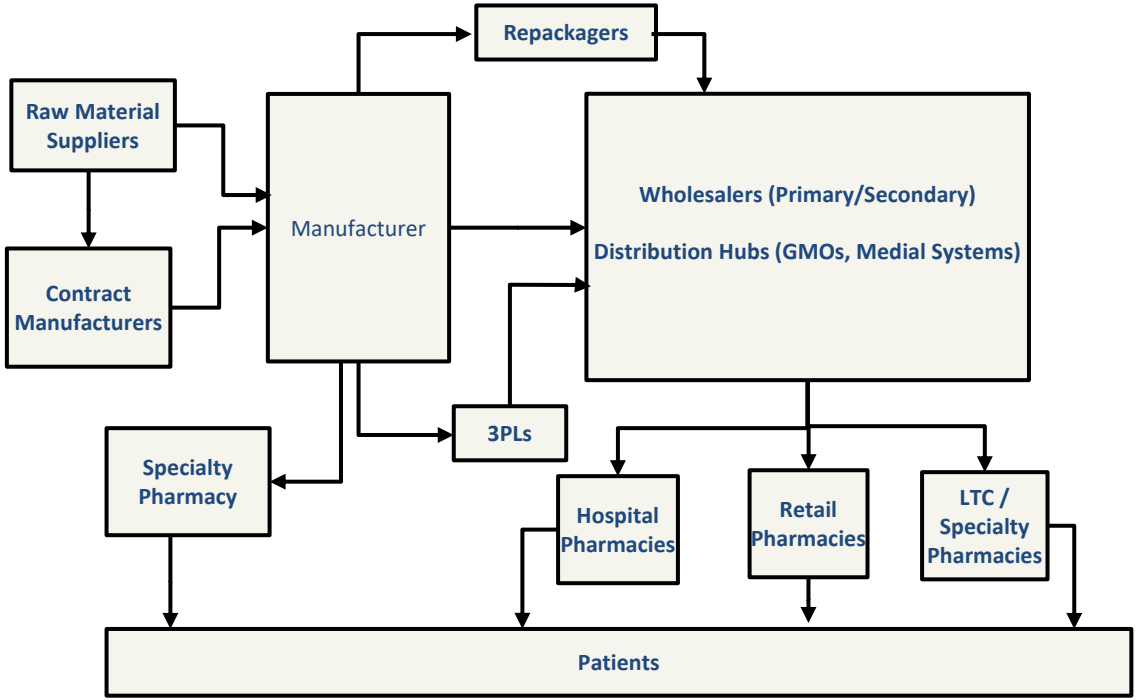
PDMA of 1987

- Addresses:
  - Reimportation and wholesale distribution of prescription drugs (pedigree requirements)
  - Sale, purchase, and trade of prescription drugs
  - Distribution of prescription drug samples

Drug Supply Chain Security Act ("DSCSA")

- Title II of the Drug Quality and Security Act of 2013
- 21 U.S.C. §§ 360eee to 360eee-4
- Applies to manufacturers, repackagers, wholesale distributors, 3PLs, and dispensers



DSCSA

- AKA “track & trace”
- State preemption
- Electronic, interoperable system to identify and trace ownership of prescription drugs
  - Chain of ownership
  - NOT chain of custody
- Combat counterfeiting, theft, contamination, etc.
- Ability to trace products will aid in quick removal of harmful products from the market

DSCSA

- Key terms:
  - "Product"
    - Approved drugs and biologics in "finished dosage form for administration to a patient without substantial further manufacturing."
    - Exclusions: Blood or blood components intended for transfusion, certain radioactive drugs or radioactive biological products imaging drugs, certain intravenous products, medical gases, homeopathic drugs or a drug compounded in compliance with section 503A or 503B.
  - "Transaction"
    - A "transfer of a product between persons in which a change of ownership occurs."
    - Exclusions: Include, but are not limited, to intracompany distributions, distributions among hospitals under common control, distributions for emergency medical reasons.

DSCSA

- Manufacturers
  - Shall provide to subsequent owner TI, TH, and TS, **"prior to, or at the time of"** each transaction in which a manufacturer **"transfers ownership of a product**," in a single document
  - Transaction Information –
    - the proprietary or established name or names of product;
    - the strength and dosage form of the product;
    - the National Drug Code number of the product;
    - the container size;
    - the number of containers;
    - the lot number of the product;
    - the date of the transaction;
    - the date of the shipment, if more than 24 hours after
    - the date of the transaction;
    - the business name and address of the person from whom ownership is being transferred; and
    - the business name and address of the person to ownership is being transferred.
  - Transaction History - a statement in paper or electronic form, including the transaction information for each prior transaction going back to the manufacturer of the product.
  - Transaction Statement - statement, in paper or electronic form, that the entity transferring ownership in a transaction:
    - is authorized as required under the Drug Supply Chain Security Act;
    - received the product from a person that is authorized as required under the Drug Supply Chain Security Act;
    - received transaction information and a transaction statement from the prior owner of the product;
    - did not knowingly ship a suspect or illegitimate product;
    - had systems and processes in place to comply with verification requirements;
    - did not knowingly provide false transaction information; and
    - did not knowingly alter the transaction history.

DSCSA

- Other requirements:
  - Product verification standards
    - » Quarantine and investigation
    - » Trading partner notifications
    - » FDA notifications
    - » Recordkeeping
  - Wholesaler and 3PL licensure standards

“Real World” Examples

Examples provided are pre-COVID but there are many examples during COVID.

Questions are welcome

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Drug Shortages

- FDA's attempt to mitigate ongoing IV saline shortages.
- Due to a critical drug shortage, FDA exercised enforcement discretion when allowing Braun to distribute its saline product in the US from its manufacturing foreign facilities.
- FDA inspected the foreign facility in Germany at least once as part of the determination to use enforcement discretion.

Failure to Pay Fees

Vista Pharmaceuticals, Ltd.

- Generic drug manufacturer
- 6/22/15 - FDA Warning Letter
  - Failed to pay appropriate facility fee as required by GDUFA
  - Placed on a publicly available GDUFA facility arrears list for failure to pay required fees in fiscal years 2013, 2014, and 2015

Failure to Register and List

A-S Medication Solutions LLC

- 6/5/17 – FDA Warning Letter
  - Drugs in the United States or that are offered for import into the United States must be registered with the FDA.
  - Every person who is required to register must, at the time of initial registration, list all drugs that are manufactured for commercial distribution.
  - Manufacturer failed to meet its registration and listing requirements.

Inaccurate Drug Listing

Exact-Rx, Inc.

- 4/19/17 - FDA Warning Letter
  - Drug listing for Sodium Sulfacetamide and Sulfer 10%/5% Cleanser is “inaccurate”
  - The listing must include, the name and quantity of each active pharmaceutical ingredient listed in the drug

Failure to Comply with REMS

- Novo Nordisk settled with the DOJ in 2017 and agreed to pay $58 million for failing to comply with FDA's REMS program.
- $46.6 million related to False Claims Act violations.
- "The REMS required Novo Nordisk to provide information regarding Victoza's potential risk of MTC to physicians. A manufacturer that fails to comply with the requirements of the REMS, including requirements to communicate accurate risk information, renders the drug misbranded under the law."
- "Sales representatives gave information to physicians that created the false or misleading impression that the Victoza REMS-required message was erroneous, irrelevant, or unimportant. The complaint further alleges that Novo Nordisk failed to comply with the REMS by creating the false or misleading impression about the Victoza REMS-required risk message that violated provisions of the FDCA and led some physicians to be unaware of the potential risks when prescribing Victoza." https://www.justice.gov/opa/pr/novo-nordisk-agrees-pay-58-million-failure-comply-fda-mandated-risk-program.

Misleading Claims About Drug Approval

Mitrasafe 2018 letter from FDA

- “FDA objects to kratom compound intended for use as an alternative to prescription opioids and promoted with unproven claims to treat addiction.”
- FDA sent a letter to Industrial Chemical LLC to notify the company that its statements about its product, Mitrasafe, are false and misleading.
- FDA’s letter states that the product is purporting to be a drug, but has not gone through the drug approval process.

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