2023 Life Sciences Summit

FDA Regulatory and Compliance Overview

DLA PIPER

Agenda

1. **Overview of FDCA and Enforcement Mechanisms**
   - Product Lifecycle: Getting a Product to Market
   - FDA's Enforcement Tools
2. **Current Good Manufacturing Practices (cGMPs)**
   - Meaning of Adulterated Products
   - FDA Inspection Trends
3. **Advertising and Promotion**
   - Meaning of Misbranded Products
   - Takeaways from Warning Letters & Untitled Letters
4. **Adverse Event Reporting**
   - Overview of Postmarketing Surveillance Requirements

FOOD AND DRUG ADMINISTRATION

Overview of Food, Drug, and Cosmetic Act (FDCA) and Enforcement Mechanisms

Key Federal Agencies

Centers for Medicare & Medicaid Services

- Payment under Medicare (Parts A, B, C and D)

HHS Office of Inspector General

- Oversees integrity of the Federal health care programs
- Compliance Guidance
- Administers Anti-Kickback Statute

Department of Justice

- False Claims Act
- Represent U.S. Government in courts

Food and Drug Administration

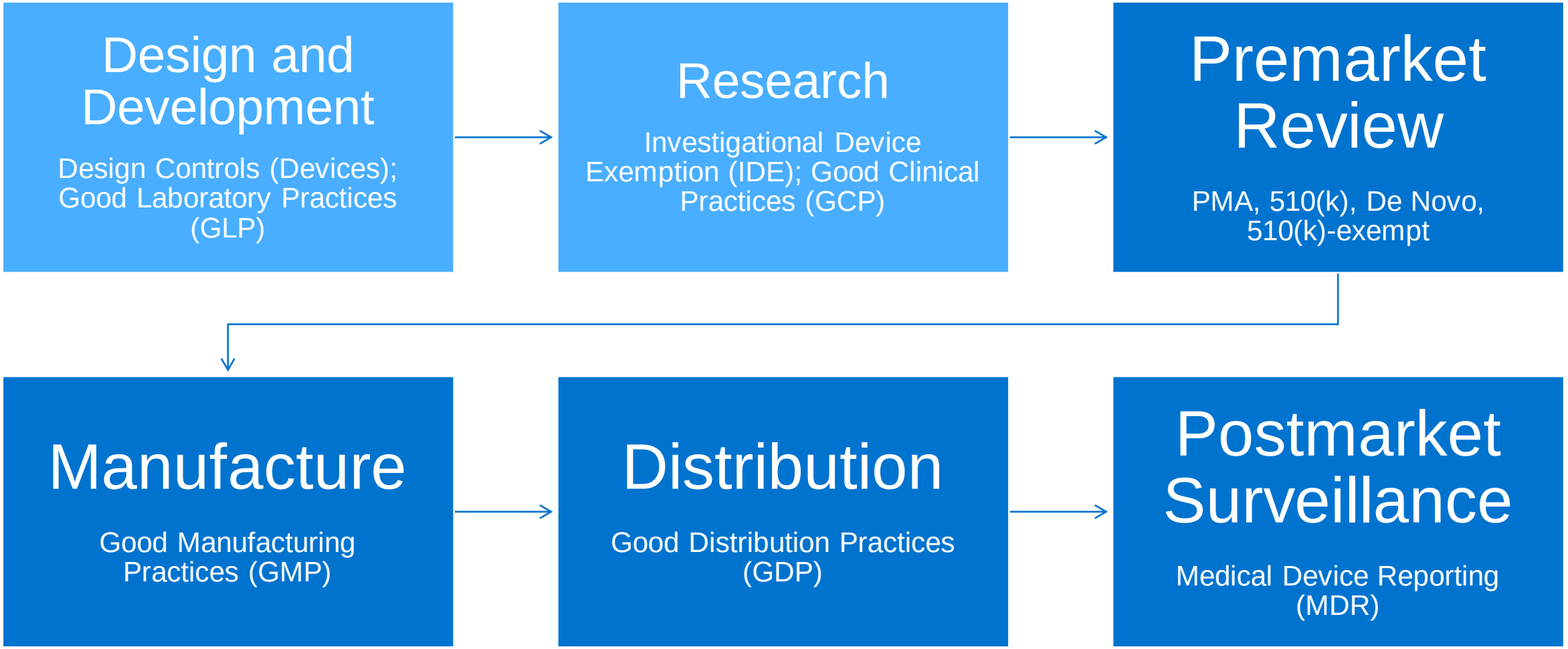
- Enforces the Food, Drug, and Cosmetic Act and implementing regulations

Scope of FDCA

- The FDCA governs the design, testing, approval, production, shipping, holding, promotion, distribution, import and export of:
  - Drugs
  - Medical devices
  - *In vitro* diagnostics
  - Food
  - Dietary supplements
  - Animal feed
  - Animal drugs and devices
  - Cosmetics
  - Tobacco products
  - Radiation emitting electronic products
- There are several FDA Centers that report to the FDA Commissioner:

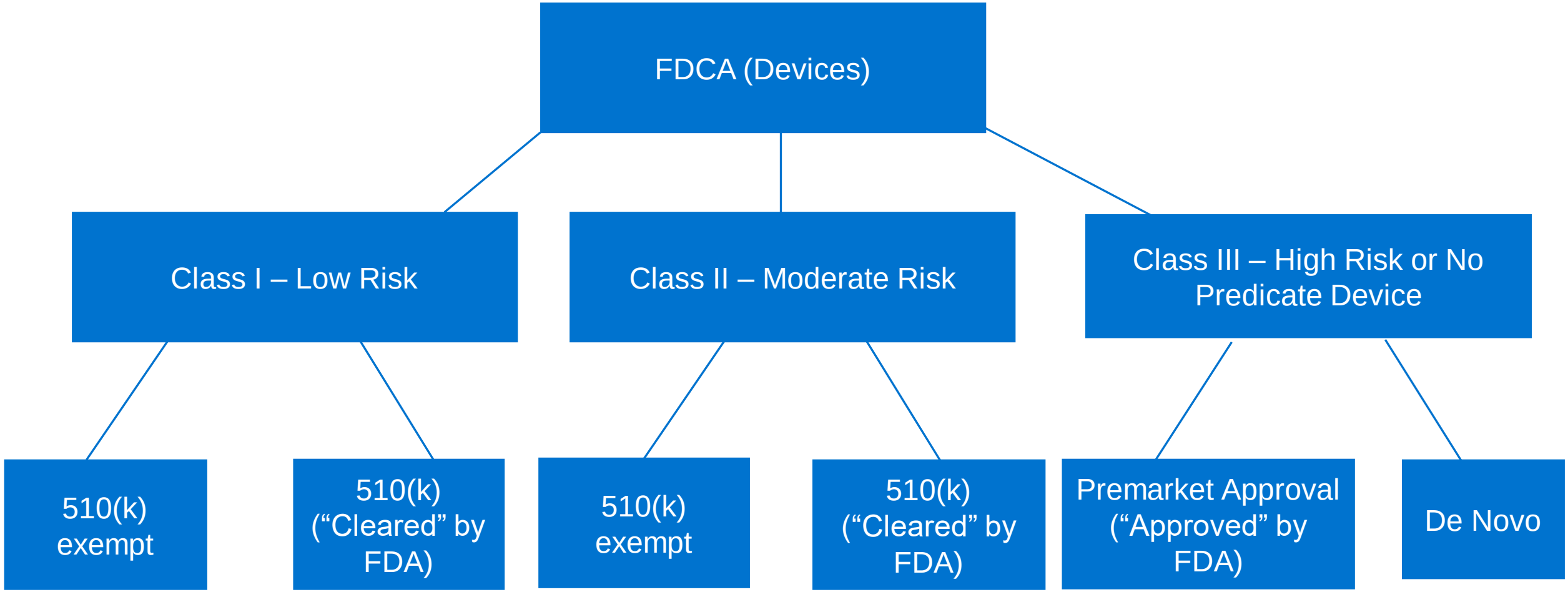
Center for Drug Evaluation & Research	Center for Devices & Radiological Health	Center for Biologics Evaluation & Research	Center for Food Safety & Applied Nutrition	Center for Tobacco Products	Center for Veterinary Medicine	Office of Regulatory Affairs

FDA Oversight in a Medical Device Life Cycle



Medical Devices: Premarket Review

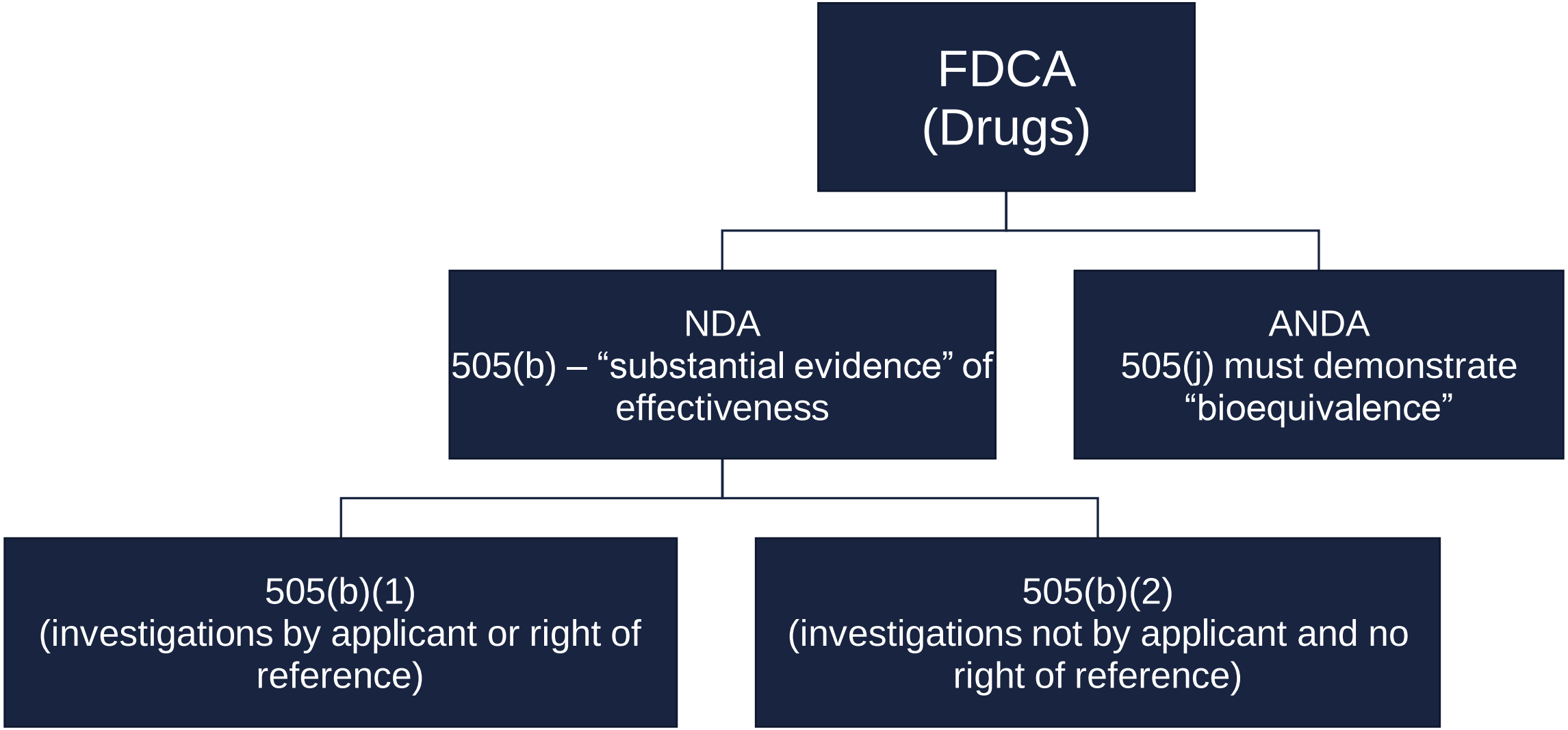
Comparing Marketing Pathways



FDA Oversight in a Drug Life Cycle

Drugs: Premarket Review

Comparing Marketing Pathways



Combination Products

- Office of Combination Products (OCP) has authority to assign an FDA center to have primary jurisdiction for review of the product.
- Combination products are assigned based on the primary mode of action (PMOA).
- PMOA refers to “the single mode of action of a combination product that provides the most important therapeutic action of the combination product. The most important therapeutic action is the mode of action expected to make the greatest contribution to the overall intended therapeutic effects of the combination product.”
- Examples:
  - Device coated or impregnated with a drug or biologic
  - Prefilled drug delivery systems (e.g., insulin injector pen, metered dose inhaler)

Key Agencies & Enforcement Tools

- FDA is the primary federal agency with authority to enforce the Federal Food, Drug, and Cosmetic Act. FDA will coordinate with DOJ for civil and criminal enforcement actions.
  - Global supply chain means OUS conduct can come under scrutiny
- Compliance and enforcement tools include:
  - Advisory Actions (e.g., Warning Letters, Untitled Letters)
  - Administrative Actions (e.g., Inspections, Recalls, Debarment, and Disqualification)
  - Enforcement Actions (e.g., Investigations, Seizures, Injunctions, Criminal or Civil Actions)

FOOD AND DRUG ADMINISTRATION

Current Good Manufacturing Practices (cGMPs)

Compliance with GMP

- Applicable Regulations:
  - For devices, current good manufacturing regulations are set forth in 21 CFR Part 820 and are referred to as “Quality System Regulations” or QSR.
  - For drugs, current good manufacturing regulations are set forth in 21 CFR Parts 210 and 211.
  - FDA has issued a number of guidance documents that describe the agency’s interpretation and current thinking of these regulations.
- Failure to follow cGMP renders the resulting product “adulterated.”

Meaning of "Adulterated" Products

Under the FDCA, there are several ways a drug or device can be deemed "adulterated" including:		
Where the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding "**do not conform to or are not operated or administered in conformity with current good manufacturing practice.**"	"strength differs from, or its purity **or quality falls below, that which it purports or is represented to possess**" (applicable to drugs)	"the owner, operator, or agent of such factory, warehouse, or establishment **delays, denies, or limits an inspection, or refuses to permit entry or inspection**"

FDA cGMP Inspections

- FDA's primary way of enforcing cGMPs is by having investigators conduct inspections at FDA-registered facilities. Activities that trigger facility registration requirement:
  - For **Drugs**: "establishment that **manufactures, repacks, relabels, or salvages** a drug, or an animal feed bearing or containing a new animal drug" (21 CFR 201.17)
  - For **Devices**: "engaged in the **manufacture, preparation, propagation, compounding, assembly, or processing** of a device" (21 CFR 807.20)
- Domestic inspections are scheduled based on a risk-based approach and are typically unannounced. Foreign inspections are preannounced in many cases but are sometimes unannounced .
- If the FDA inspector observes deficiencies at the facility, they will issue a Form FDA 483, which will list out each of the observations. The company must respond in writing within 15 business days.

Common GMP Violations based on 2009-2022 Inspection Data

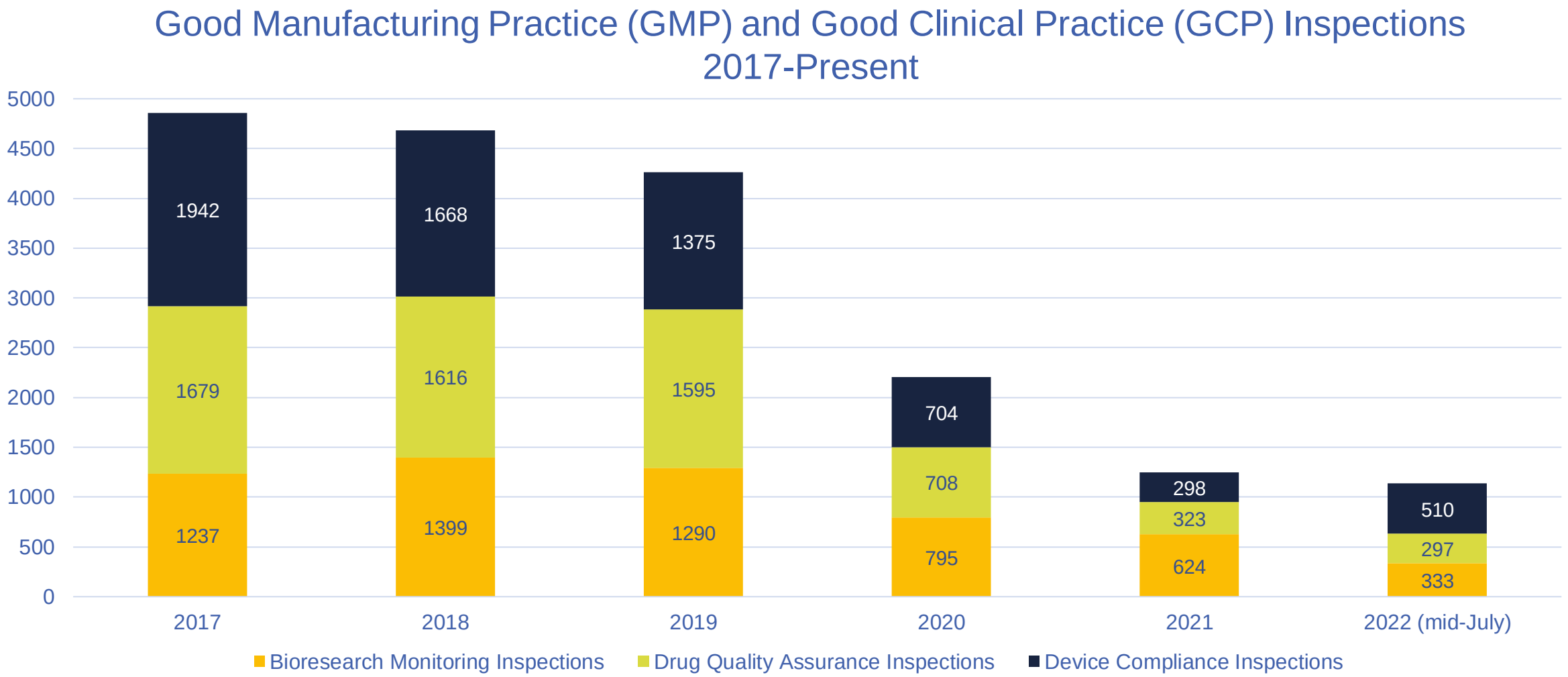
Medical Devices

- Written procedures (21 CFR 820.100)
- Complaint procedures (21 CFR 820.198)
- Purchasing controls (21 CFR 820.50)
- Process validation (21 CFR 820.75)
- Controls over nonconforming product (21 CFR 820.90)

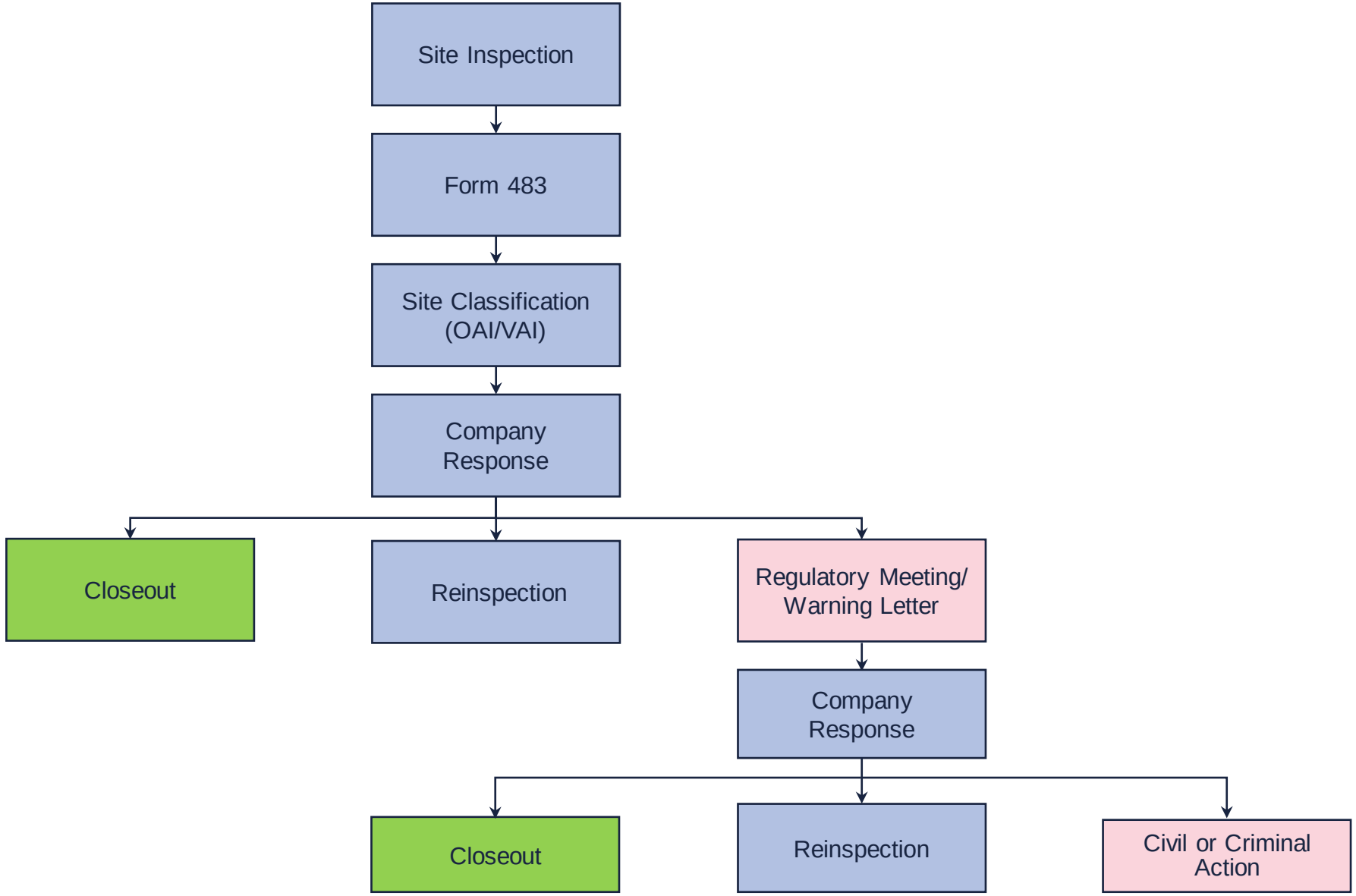
Drugs

- Lack of written procedures, or procedures not being fully followed (21 CFR 211.22, 211.100)
- Scientifically sound laboratory controls (21 CFR 211.160)
- Investigations of discrepancies and failures (21 CFR 211.192)
- Testing and release for distribution (21 CFR 211.165)
- Cleaning, sanitizing, and maintenance (21 CFR 211.67)

Regulatory Environment



Site Inspection and Escalation Flow Chart



Recalls

Grounds for Recall	As defined in FDA regulations, “a firm's removal or correction of a marketed product that the Food and Drug Administration considers to be in violation of the laws it administers and against which the agency would initiate legal action, e.g., seizure.”
Process	Recalls are typically carried out voluntarily by manufacturer. In rare instances where manufacturer fails to voluntarily recall a product that poses a risk to public health, FDA may issue a mandatory recall order to the manufacturer (in some but not all product contexts).
Classifications	Class I: a situation in which there is a reasonable probability that the use of, or exposure to, a violative product will cause serious adverse health consequences or death. Class II: a situation in which use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote. Class III: a situation in which use of, or exposure to, a violative product is not likely to cause adverse health consequences.

FOOD AND DRUG ADMINISTRATION

Advertising and Promotion

FEDERAL TRADE COMMISSION

Regulation of Promotion and Advertising

FDA regulates the labeling of all medical devices and drugs

For advertising, jurisdiction is split:

FDA: Rx drugs and “restricted” devices

FTC: OTC drugs and non-restricted devices

Key Terms

- **Label:** “a display of written, printed, or graphic matter upon the immediate container of any article.” 21 U.S.C. § 321(k)
- **Labeling**: “[a]ll labels and other written, printed or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article.” 21 U.S.C. § 321(m)
- **Advertising:** not formally defined but would include, for example, journals, publications, and radio, TV, and print ads.

“The distinction between labeling and advertising, both of which draw attention to the article to be sold, is often superficial or nebulous. Both are used for a similar purpose, i.e., to provide information about the product. Thus, according to an appellate court decision: **‘Most, if not all advertising, is labeling.’”** –FDA Guidance

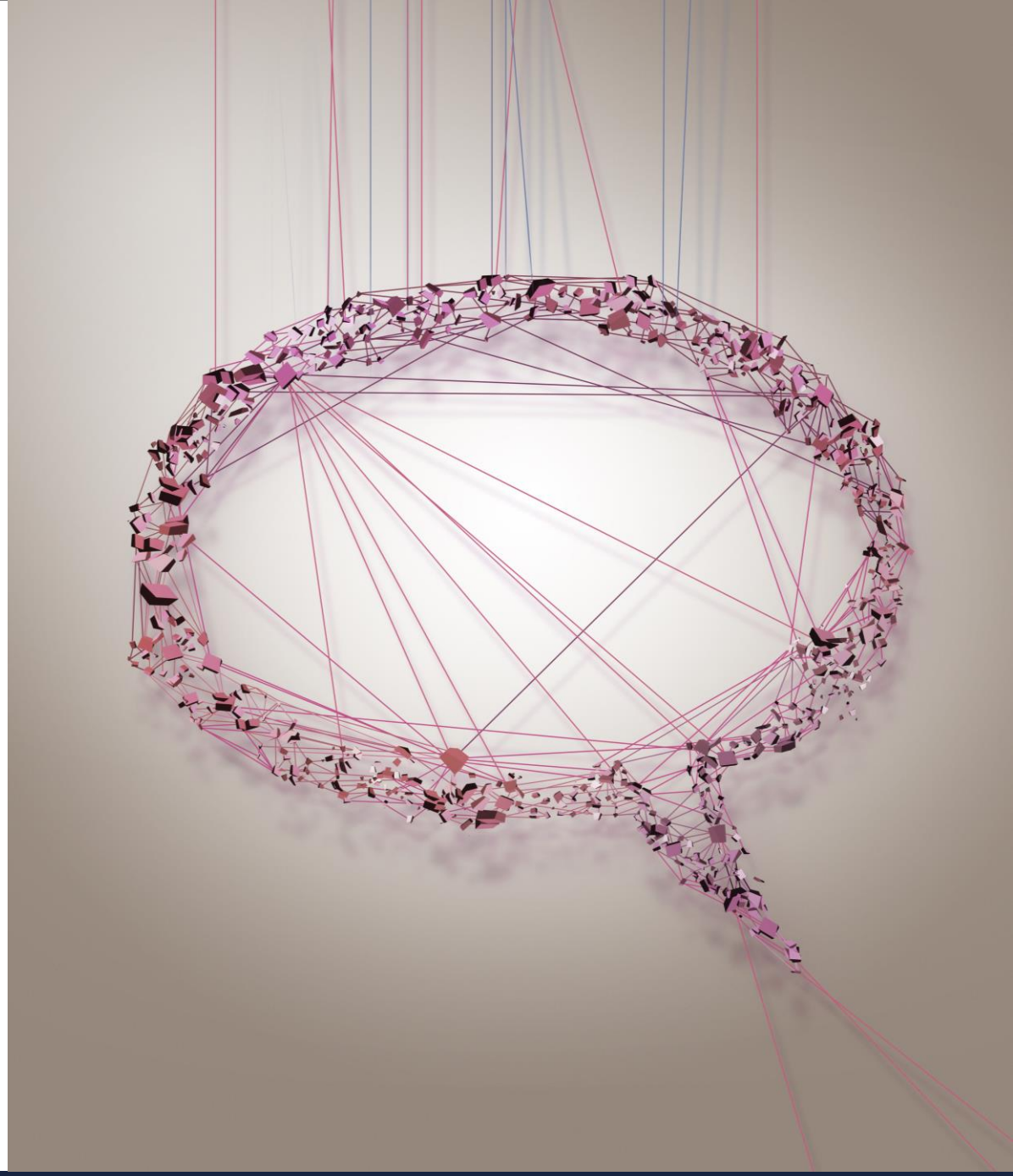
Meaning of "Misbranded"

Under the FDCA, there are several ways a drug or device can be deemed "misbranded" including:

Where the labeling is **"false or misleading in any particular"**	Label **does not bear adequate directions for use and warnings**	Package **fails to contain the name and place of business** of manufacturer, packer, or distributor; **or an accurate statement of quantity of contents**	Drug is **health-endangering when used as prescribed, recommended, or suggested** in the labeling

Meaning of “Intended Use”

- As defined in FDA regulations (21 C.F.R 801.4; 201.128), “intended use” refers to the “objective intent” of the persons legally responsible for the labeling of devices and drugs.
- Intent can be shown via:
  - labeling claims
  - advertising matter
  - oral or written statements by persons or their representatives
  - circumstances surrounding the distribution of the article



How do FDA and FTC “find” violative ads?

- FDA attendance at conferences, expos, and booths
- FDA surveillance – online, print, TV
- Competitor complaints
- HCP complaints
- National Advertising Division (NAD) complaints

Warning Letter to CytoDyn, Inc.

February 2022

Promotion of Pipeline Products

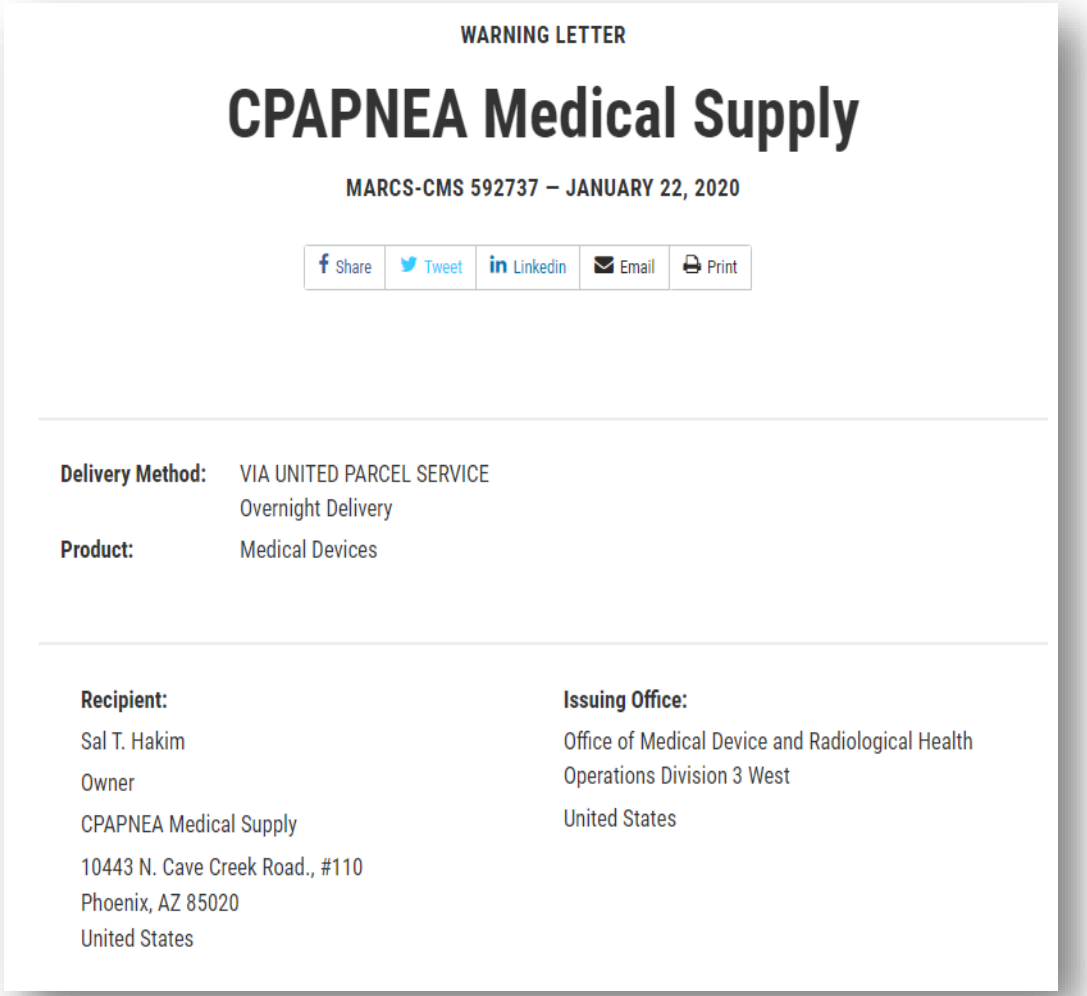
- Office of Prescription Drug Promotion (OPDP) issued a warning letter based on a Youtube video featuring the former President/CEO of CytoDyn, Dr. Nader Pourhassan, who made certain statements about leronlimab, an investigational COVID-19 treatment.
- OPDP alleged that the former executive made "conclusory statements" about the safety and efficacy of the investigational product (e.g., "**our results were really strong**…" and "when we gave a dose of leronlimab, **the survival rate was 78%**. Once we gave them another dose, **the survival rate went up to 82%")**.
- OPDP alleged that the video "significantly mischaracterizes" the clinical trial data given that the larger trial conducted in patients with severe COVID-19 disease "failed to find **any** effect" (emphasis by OPDP) on the primary study endpoint or any secondary endpoints.

Warning Letter to CPAPNEA Medical Supply

January 2020

Off-Label Promotion

- CPAPNEA Medical Supply has a cleared 510(k), K181219, for the Optipillows EPAP mask for the sole intended use of **alleviating snoring** during sleep in adults.
- Based on materials collected during inspection and website review, CDRH alleged that the EPAP mask was misbranded because the product was promoted beyond its cleared use, i.e., the company claimed that its product could treat **obstructive sleep apnea and that it could be used as a substitute for Continuous Positive Airway Pressure (CPAP) devices.**
- Marketing of the product in this manner constituted a "major change or modification" that required the submission of a new 510(k) submission.



WARNING LETTER

CPAPNEA Medical Supply

MARCS-CMS 592737 – JANUARY 22, 2020

Share Tweet Linkedin Email Print

Delivery Method: VIA UNITED PARCEL SERVICE
Overnight Delivery

Product: Medical Devices

Recipient:
Sal T. Hakim
Owner
CPAPNEA Medical Supply
10443 N. Cave Creek Road., #110
Phoenix, AZ 85020
United States

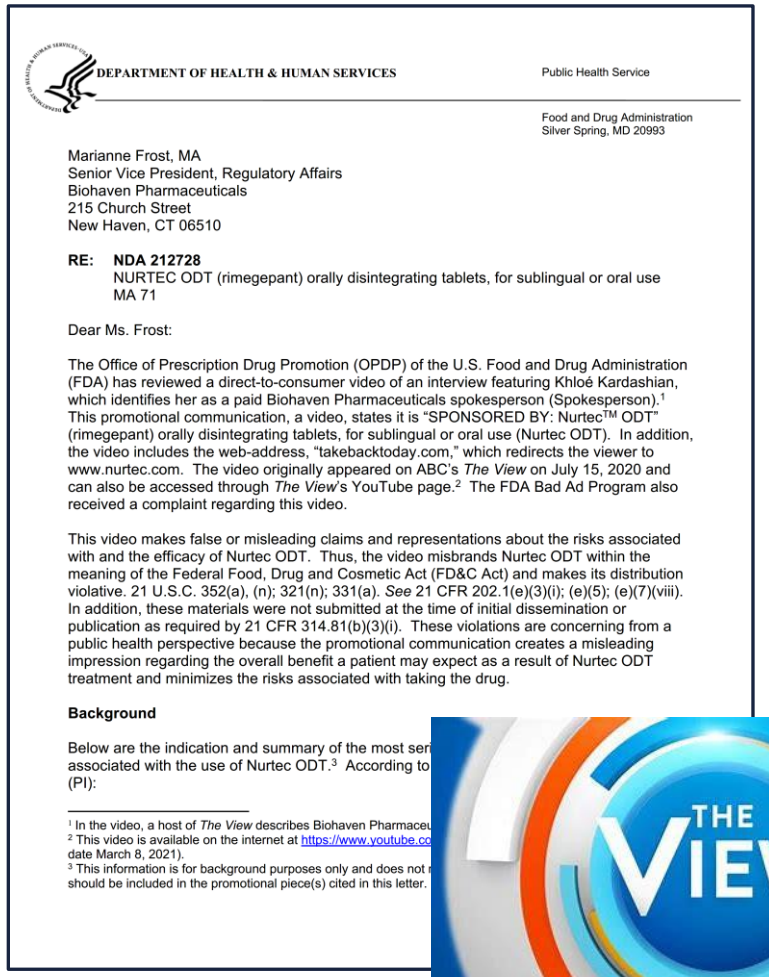
Issuing Office:
Office of Medical Device and Radiological Health
Operations Division 3 West
United States

Untitled Letter to Biohaven Pharmaceuticals

March 2021

Comparative Claims

- **Background**
  - DTC video of an interview with spokesperson Khloe Kardashian regarding migraine medication (Nurtec)
  - Video reviewed by FDA and complaint received via FDA Bad Ad Program
- **FDA Findings**
  - Unsupported efficacy claims and comparative claims (even if spokesperson is discussing her own experience)
  - Failed to adequately communicate
    - ➢ Full FDA-approved indication and limitations of use
    - ➢ Contraindications and adverse events
    - ➢ Safety information



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Marianne Frost, MA
Senior Vice President, Regulatory Affairs
Biohaven Pharmaceuticals
215 Church Street
New Haven, CT 06510

RE: NDA 212728
NURTEC ODT (rimegepant) orally disintegrating tablets, for sublingual or oral use
MA 71

Dear Ms. Frost:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed a direct-to-consumer video of an interview featuring Khloé Kardashian, which identifies her as a paid Biohaven Pharmaceuticals spokesperson (Spokesperson).[1] This promotional communication, a video, states it is "SPONSORED BY: Nurtec™ ODT" (rimegepant) orally disintegrating tablets, for sublingual or oral use (Nurtec ODT). In addition, the video includes the web-address, "takebacktoday.com," which redirects the viewer to www.nurtec.com. The video originally appeared on ABC's *The View* on July 15, 2020 and can also be accessed through *The View*'s YouTube page.[2] The FDA Bad Ad Program also received a complaint regarding this video.

This video makes false or misleading claims and representations about the risks associated with and the efficacy of Nurtec ODT. Thus, the video misbrands Nurtec ODT within the meaning of the Federal Food, Drug and Cosmetic Act (FD&C Act) and makes its distribution violative. 21 U.S.C. 352(a), (n); 321(n); 331(a). *See* 21 CFR 202.1(e)(3)(i); (e)(5); (e)(7)(viii). In addition, these materials were not submitted at the time of initial dissemination or publication as required by 21 CFR 314.81(b)(3)(i). These violations are concerning from a public health perspective because the promotional communication creates a misleading impression regarding the overall benefit a patient may expect as a result of Nurtec ODT treatment and minimizes the risks associated with taking the drug.

Background

Below are the indication and summary of the most ser
associated with the use of Nurtec ODT.[3] According to
(PI):

[1] In the video, a host of *The View* describes Biohaven Pharmaceu
[2] This video is available on the internet at https://www.youtube.co
date March 8, 2021).
[3] This information is for background purposes only and does not
should be included in the promotional piece(s) cited in this letter.

Warning Letter to AstraZeneca Pharmaceuticals LP

August 2023

Presentation of Clinical Trial Results

- FDA/OPDP: Efficacy claims contained in an AstraZeneca sales aid for BREZTRI AEROSPHERE™ (budesonide, glycopyrrolate, and formoterol fumarate) inhalation aerosol (indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD)) regarding a reduction in all-cause mortality and a significant reduction in severe exacerbations were not supported by the cited trial data, and therefore created a misleading impression regarding the overall benefits a patient may expect as a result of treatment with the drug.

- AstraZeneca requested to disseminate truthful, non-misleading, and complete corrective communications.

FOOD AND DRUG ADMINISTRATION

Adverse Event Reporting

Medical Device Reporting (MDR)

30-day Reports

Deaths or serious injuries

Malfunctions that would likely cause or contribute to death or serious injury if recurred

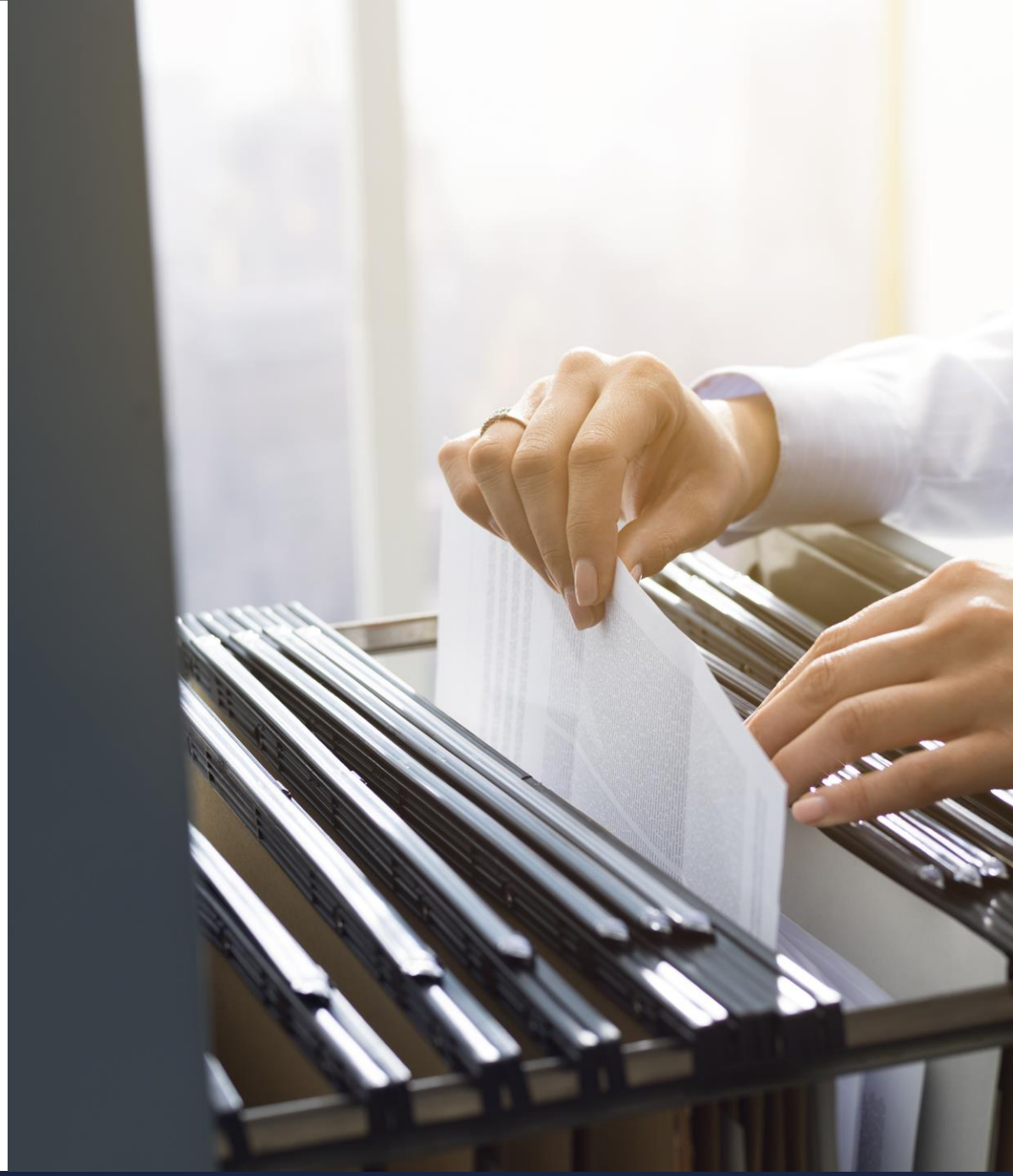
5-day Reports

To prevent unreasonable risk of substantial harm to public health

Reportable events for which FDA has made a written request

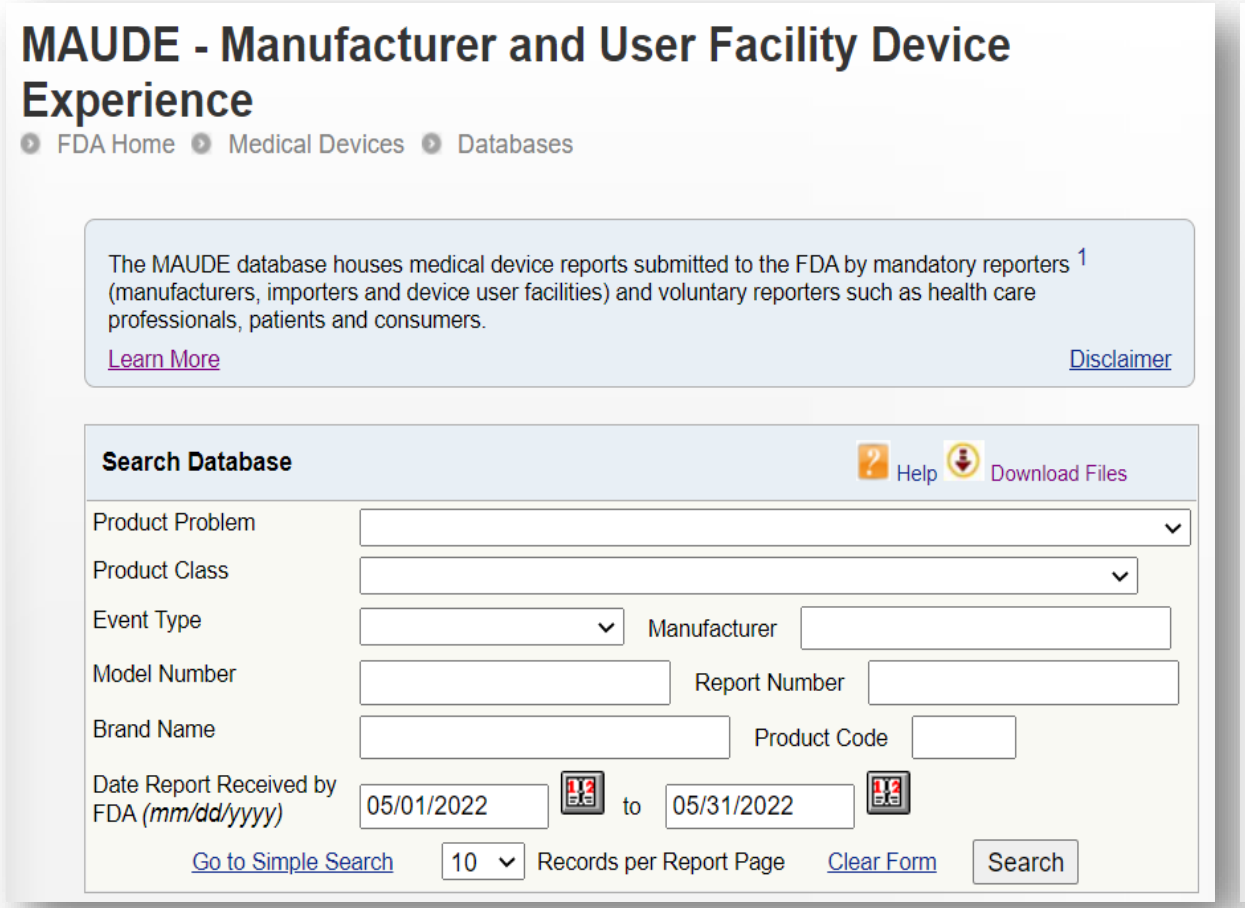
MDR Procedural Requirements

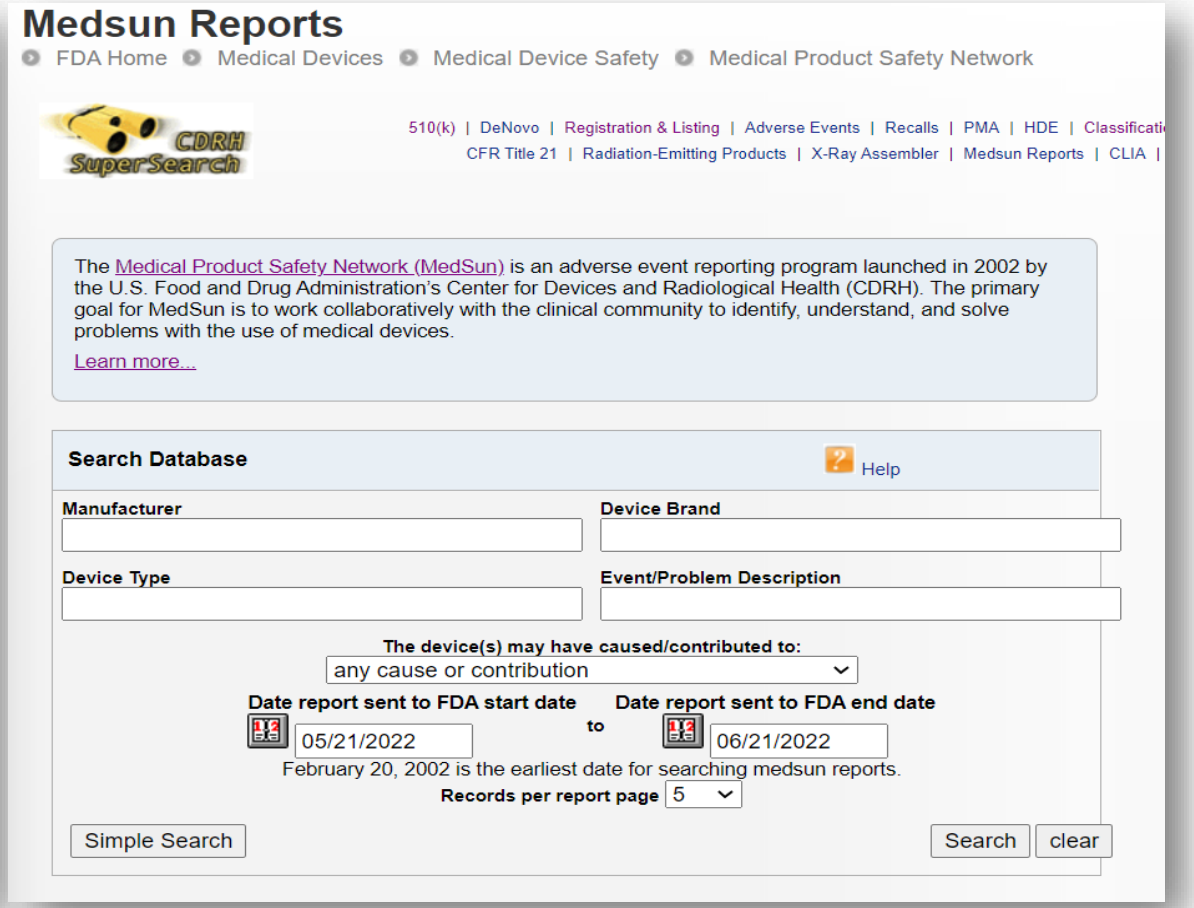
- Manufacturers should maintain and follow procedures to ensure:
  - (1) timely and effective identification, communication, and evaluation of events that may be subject to MDR requirements;
  - (2) a standardized review process or procedure for determining when an event meets the criteria for reporting under this part; and
  - (3) timely transmission of complete medical device reports to FDA (or the manufacturer, if applicable).



For Devices: MAUDE and MedSun

Public Databases with Adverse Event Data on Medical Devices





Drug Safety Reporting Requirements

15-day reports

Both “serious” and “unexpected” adverse events from all sources

Applies to domestic and foreign adverse events

Periodic Safety Update Reports (PSUR)

Required quarterly for first 3 years after US approval,

After 3 years, sponsor must submit PSUR annually

For Drugs: FDA Adverse Event Reporting System (FAERS)

- FAERS is a computerized database that collects spontaneous adverse event reports, medication error reports and product quality complaints resulting in adverse events that were submitted to FDA.
  - Drug manufacturers are **required** to submit reports
  - HCPs and consumers **may voluntarily** submit reports
- The reports in FAERS are evaluated by clinical reviewers in CDER who monitor the safety of products after they are approved by FDA.
- Based on an evaluation of FAERS data, FDA may update a product's labeling information, restrict the use of the drug, communicate new safety information to the public, or, in rare cases, remove a product from the market.

Limitations on Adverse Event Reporting Databases

- "FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. . .There are also duplicate reports . . . **Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.**"
- "In addition, although MDRs are a valuable source of information, this passive surveillance system has limitations. The **incidence, prevalence, or cause of an event cannot be determined from this reporting system alone** due to under-reporting of events, inaccuracies in reports, lack of verification that the device caused the reported event, and lack of information about frequency of device use."

Questions and Answers on FDA's Adverse Event Reporting System (FAERS) | FDA; About Manufacturer and User Facility Device Experience (MAUDE) | FDA

Thank you