Naltrexone Injection for Opioid Use Disorder: FDA's Efforts to Reduce Medication Errors

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CDR Jessica Voqui is a pharmacist officer in the U.S. Public Health Service (USPHS) and serves as the Associate Director for Postmarket Regulatory Science in the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) within the Office of New Drugs in the U.S. Food and Drug Administration's (FDA's) Center for Drug Evaluation and Research. CDR Voqui is the division-level expert responsible for technical oversight of postmarket regulatory science actions for drug safety in DAAP, including actions related to opioid analgesics and products used to treat opioid use disorder.

CDR Voqui earned her Doctor of Pharmacy degree from Virginia Commonwealth University School of Pharmacy; earned a Master of Science degree through the Pharmaceutical Outcomes and Policy Graduate Program at the University of Florida; and obtained the Regulatory Affairs Certification in 2022. Before joining her current division, she began her FDA career by serving in diverse positions across the Office of New Drugs, on the Clinical Outcome Assessments Staff and the Biomedical Informatics and Regulatory Review Science Team.

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Dr. Sofanit Getahun is a Safety Evaluator, with the Division of Medication Error Prevention and Analysis1 (DMEPA 1), Office of Medication Error Prevention and Risk Mitigation (OMEPRM), Office of Surveillance and Epidemiology (OSE), Center for Drug Evaluation and Research (CDER), at the U.S. Food and Drug Administration (FDA). Dr. Getahun is part of a multidisciplinary team responsible for reviewing and analyzing medication errors and providing expertise within FDA and to external organizations to assess the risk of medication errors throughout a product's lifecycle, from preapproval to post approval.

Dr. Getahun earned her degree of Doctor of Pharmacy from the University of Maryland Baltimore School of Pharmacy in 2006. She has been a practicing clinical pharmacist for the past 17 years. Prior to joining the Agency, she has worked at the University of Maryland Medical Center in Baltimore (UMMC) and The Children's National Hospital in Washington, DC. At UMMC she has worked at numerous levels within the pharmacy department. In 2018 she transitioned to The Children's National Hospital in Washington, DC where she is currently active as a clinical pharmacist.

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CDR Mark A. Liberatore is a pharmacist officer in the U.S. Public Health Service (USPHS). He currently serves as the Deputy Director for Safety in the Division of Anesthesiology, Addiction Medicine, and Pain Medicine within the Office of New Drugs in the U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research.

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Disclosures

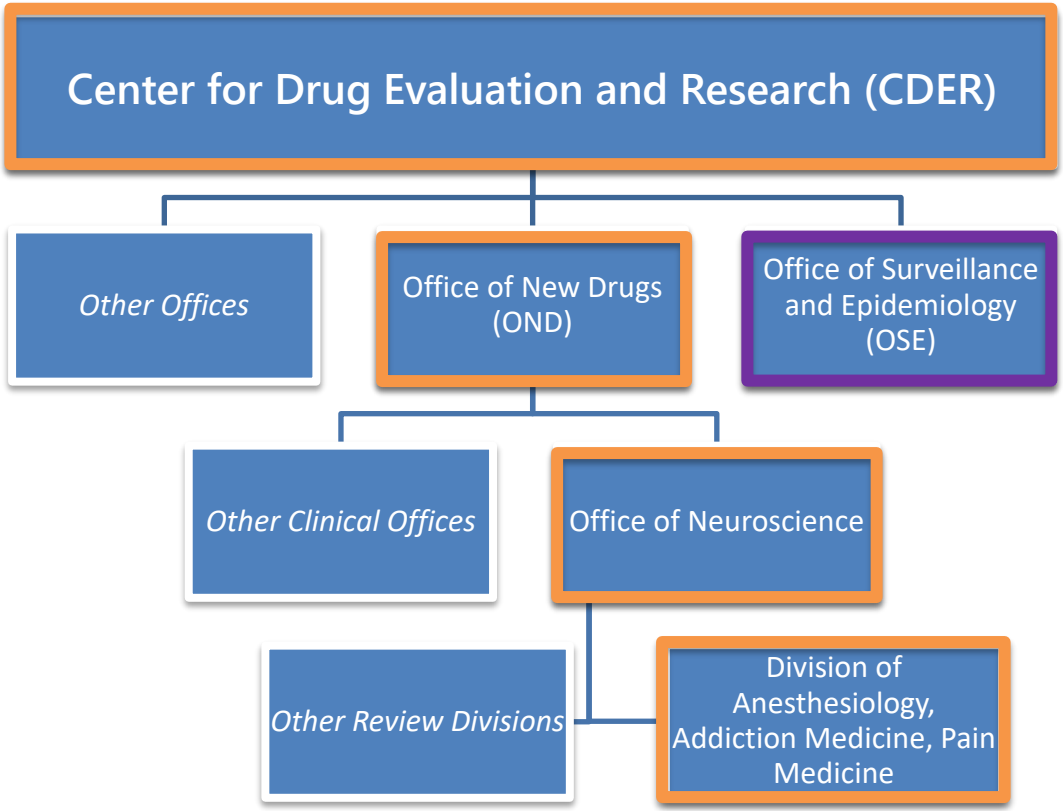
- CDR Voqui, Dr. Getahun, CDR Liberatore, and LCDR Vaughan have no relevant financial or non-financial relationships to disclose relating to the content of this activity.
- The views expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of the Department of Defense, FDA, nor the U.S. Government.
- This continuing education activity is managed and accredited by the Defense Health Agency, J-7, Continuing Education Program Office (DHA, J-7, CEPO). DHA, J-7, CEPO and all accrediting organizations do not support or endorse any product or service mentioned in this activity.
- DHA, J-7, CEPO staff, as well as activity planners and reviewers have no relevant financial or non-financial interest to disclose.
- Commercial support was not received for this activity.

Learning Objectives

At the conclusion of this activity, participants will be able to:

1. Discuss the opioid crisis and importance of medications used to treat opioid use disorder.
2. Describe postmarket drug safety authorities and postmarket medication error surveillance.
3. Illustrate how FDA's process for identifying and evaluating postmarket safety issues is applied for medication errors.
4. Explain how postmarket safety information can be used to change product labeling.
5. Summarize how healthcare providers can contribute to drug safety within their practice.

Organizational Chart

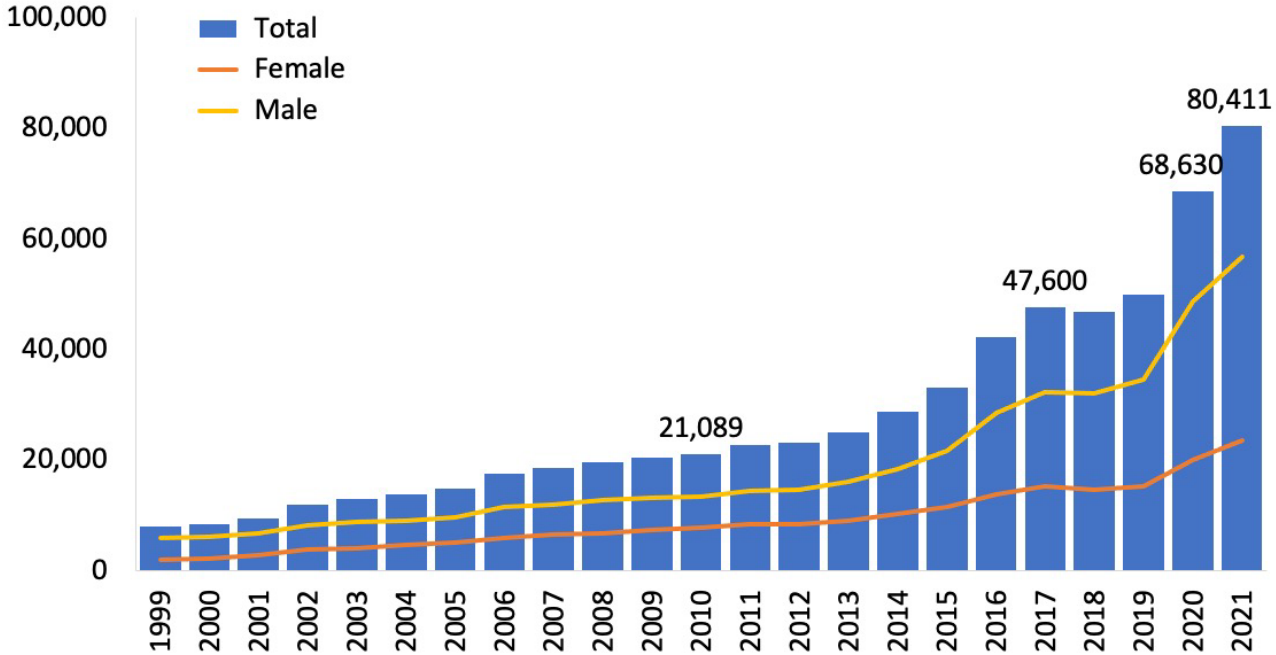


Division of Anesthesiology, Addiction Medicine, and Pain Medicine

Regulates and reviews Investigational New Drug Applications (INDs), New Drug Applications (NDAs), and Biologics Licensing Applications (BLAs) for prescription drugs and biologics intended for the prevention, treatment, or diagnosis of conditions including:

- **Anesthesiology**
  - Anesthetics (general, local, dental, topical)
  - Neuromuscular-blocking agents and neuromuscular-blocker reversal agents
- **Addiction** (e.g., nicotine, alcohol, stimulants, opioids)
- **Pain**
  - Acute (e.g., surgical and procedural pain, pain due to trauma/injury, pain due to acute inflammatory processes)
  - Chronic (e.g., pain related to cancer, neuropathy, fibromyalgia, osteoarthritis, low back pain).

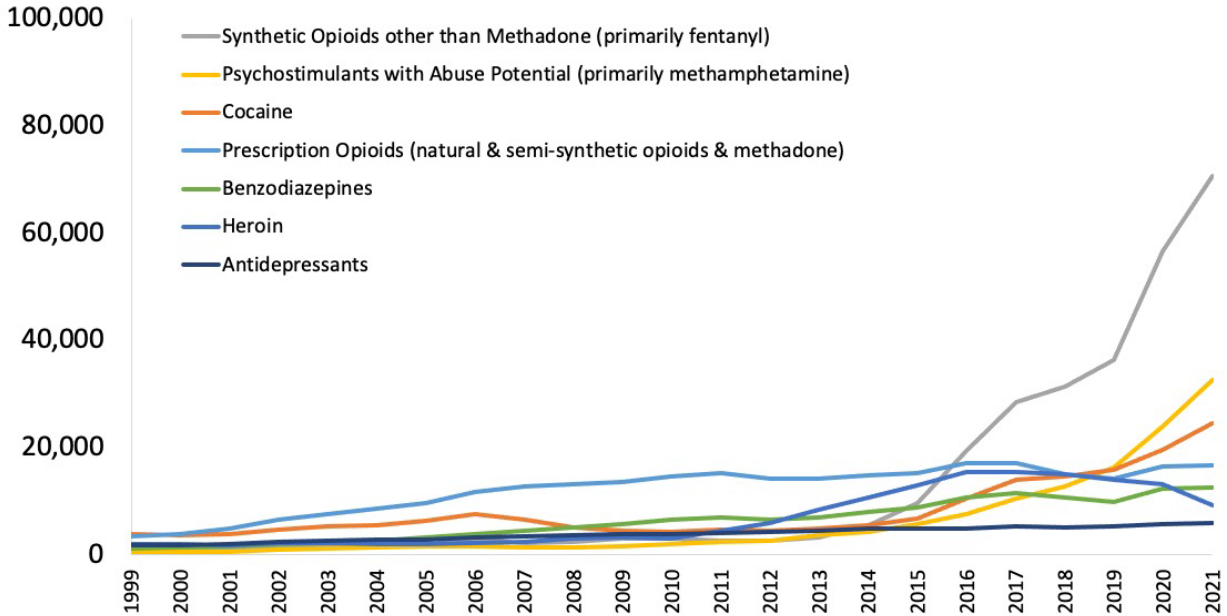
Figure 3. National Overdose Deaths Involving Any Opioid*, Number Among All Ages, by Gender, 1999-2021



*Among deaths with drug overdose as the underlying cause, the "any opioid" subcategory was determined by the following ICD-10 multiple cause-of-death codes: natural and semi-synthetic opioids (T40.2), methadone (T40.3), other synthetic opioids (other than methadone) (T40.4), or heroin (T40.1). Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

(U.S. Department of Health and Human Services, 2023)

Figure 2. National Drug-Involved Overdose Deaths*, Number Among All Ages, 1999-2021



*Includes deaths with underlying causes of unintentional drug poisoning (X40–X44), suicide drug poisoning (X60–X64), homicide drug poisoning (X85), or drug poisoning of undetermined intent (Y10–Y14), as coded in the International Classification of Diseases, 10th Revision. Source: Centers for Disease Control and Prevention, National Center for Health Statistics. Multiple Cause of Death 1999-2021 on CDC WONDER Online Database, released 1/2023.

(U.S. Department of Health and Human Services, 2023)

U.S. Department of Health & Human Services – Overdose Prevention Strategy

Primary Prevention	Preventing substance use disorder is the first step towards addressing overdoses.
Harm Reduction	Harm reduction is critical to keeping people who use drugs alive and as healthy as possible.
Evidence-Based Treatment	When a person is ready, high-quality treatment must be available without delay.
Recovery Support	Recovery support services can lead to better long-term outcomes, especially when available in communities where they are needed.

(U.S. Department of Health and Human Services, 2024)

Currently Approved Medications Used to Treat Opioid Dependence

- **Buprenorphine**
  - Sublingual tablet
  - Subcutaneous injection
  - Subdermal implant
  - Extended-release subcutaneous injection
  - Combination buprenorphine and naloxone
    - buccal film
    - sublingual film or tablet
- **Methadone**
  - Tablets
  - Oral liquid concentrate
- **Naltrexone**
  - Extended-release (suspension) intramuscular injection

(U.S. Food and Drug Administration, 2023)

Naltrexone Extended-Release Suspension for Injection

- Mechanism of action: *mu*-opioid receptor antagonist
  - Note: Prior to initiating treatment, an opioid-free duration of a minimum of 7-10 days is recommended for patients, to avoid precipitation of withdrawal that may be severe enough to require hospitalization.
- Route of administration: Intramuscular, extended-release injectable suspension
- Frequency: Injected every 4 weeks or once a month
- Indicated for:
  - **Alcohol Dependence**: The treatment of alcohol dependence in patients who are able to abstain from alcohol in an outpatient setting prior to initiation of treatment with VIVITROL. Patients should not be actively drinking at the time of initial VIVITROL administration.
  - **Opioid Dependence**: Prevention of relapse to opioid dependence, following opioid detoxification.
  - *For both indications – treatment should be part of a comprehensive management program that includes psychosocial support*

Food and Drug Administration Amendments Act of 2007 (FDAAA)

Title IX: Enhanced Postmarket Safety Authorities

Section 901 of FDAAA amended Section 505 of the Federal Food, Drug, and Cosmetic Act to provide the Agency with substantial new authorities to ensure the safe and appropriate use of drugs to:

- Require postmarketing studies and clinical trials through **Postmarketing Requirements (PMRs)**
- Require applicants to establish and comply with a **Risk Evaluation and Mitigation Strategy (REMS)**
- Require applicants to make **safety labeling changes (SLCs)**

Risk Evaluation and Mitigation Strategy (REMS)

- A REMS is a drug safety program that FDA can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.
- A REMS is required *before* approval if FDA determines a REMS is necessary to ensure that the benefits of a drug outweigh the risks or *post-approva*l if FDA becomes aware of new safety information.
  - Represents additional risk management beyond labeling
  - A REMS is an enforceable document describing the elements that a drug company (NDA holder) must implement
- A REMS may include:
  - Medication Guide or Patient Package Insert
  - Communication Plan for Healthcare Providers
  - Certain packaging and safe disposal technologies for drugs that pose a serious risk of abuse or overdose
  - Elements to Assure Safe Use (ETASU)
  - Implementation System
- A REMS must include a timetable for submission of assessments of the REMS.

(Federal Food, Drug, and Cosmetic Act, 2023)

Safety Labeling Changes (SLC)

Section 505(o)(4) authorizes FDA to require, and if necessary, *order* changes to labeling based on the *new safety information* or new effectiveness information.

- Scope: Prescription drug or biologic products and certain generic Rx products.
- SLC action is required if the FDA becomes aware of new information, including any *new safety information* or information related to reduced effectiveness, that the FDA determines should be included in the labeling of the drug.

Also refer to *Guidance for Industry: Safety Labeling Changes -- Implementation of Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act*, 2013, at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-labeling-changes-implementation-section-505o4-federal-food-drug-and-cosmetic-act.

Regulatory Definition of *New Safety Information*

Section 505-1(b) defines ***new safety information*** as:

- information derived from a clinical trial, an adverse event report, a post approval study, peer-reviewed biomedical literature, data derived from the postmarket risk identification and analysis system (i.e., FAERS); or other scientific data deemed appropriate by [FDA] about:
  - A **serious risk or an unexpected serious risk associated with use of the drug** that [FDA] has become aware of since the drug was approved, since the risk evaluation and mitigation strategy (REMS) was required, or since the last assessment of the approved [REMS] for the drug, or
  - The effectiveness of the approved [REMS] for the drug obtained since the last assessment of [the REMS].

Types of labeling changes that could be required are generally, but not limited to:

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/YYYY
Section Title, Subsection Title (x.x) M/YYYY

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a *[[insert FDA established pharmacologic class text phrase]]* indicated for … (1)

Limitations of Use
Text (1)

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
Dosage form(s): strength(s) (3)

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
- Text (8.x)
- Text (8.x)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling OR and Medication Guide

Revised: M/YYYY

(https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/prescribing-information-resources)

General Process for Postmarket Safety Regulatory Actions Under Section 505

Identification of New Safety Information (NSI)

FDA becomes aware of NSI and determines that regulatory action is needed.

For example, if the NSI:

- Should be included in labeling → **SLC**
- Supports that a REMS is necessary to ensure that the benefits of a drug outweigh the risks after the drug is approved* → **REMS**
- Supports that a postmarketing trial or study is required to better understand the risk of the safety issue → **PMR**

Initiate Action

FDA will notify the Application holder (drug company) of the drug or biologic product with NSI and required action (with specified timeframe).

Examples of required submission:

- **SLC**: Updated labeling or rebuttal, if applicable
- **REMS**: REMS proposal
- **PMR**: Milestone submissions (Draft/Final Protocol, Final Study Report, etc.)

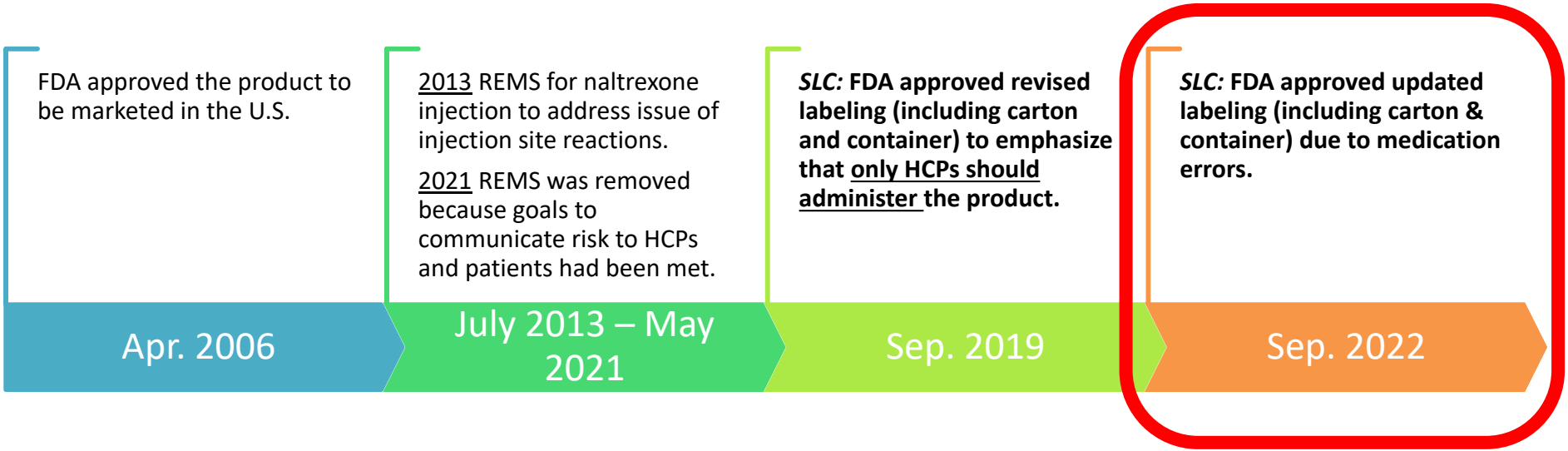
*REMS may also be required before the drug is approved if FDA determines it is necessary to ensure the benefits outweigh the risks

Finalize Action

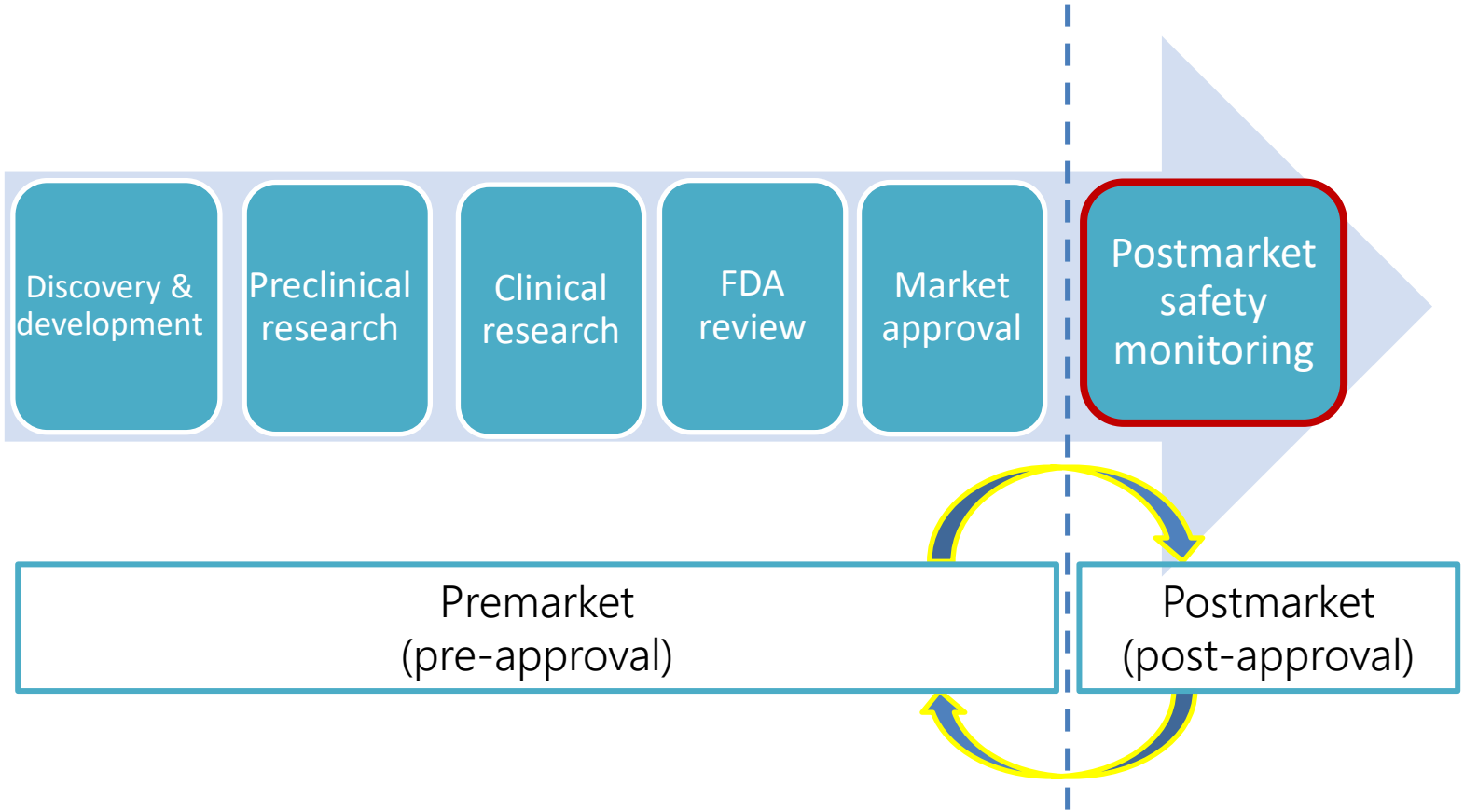
Applicant submits their response and FDA will review the submission(s) and take appropriate action(s).

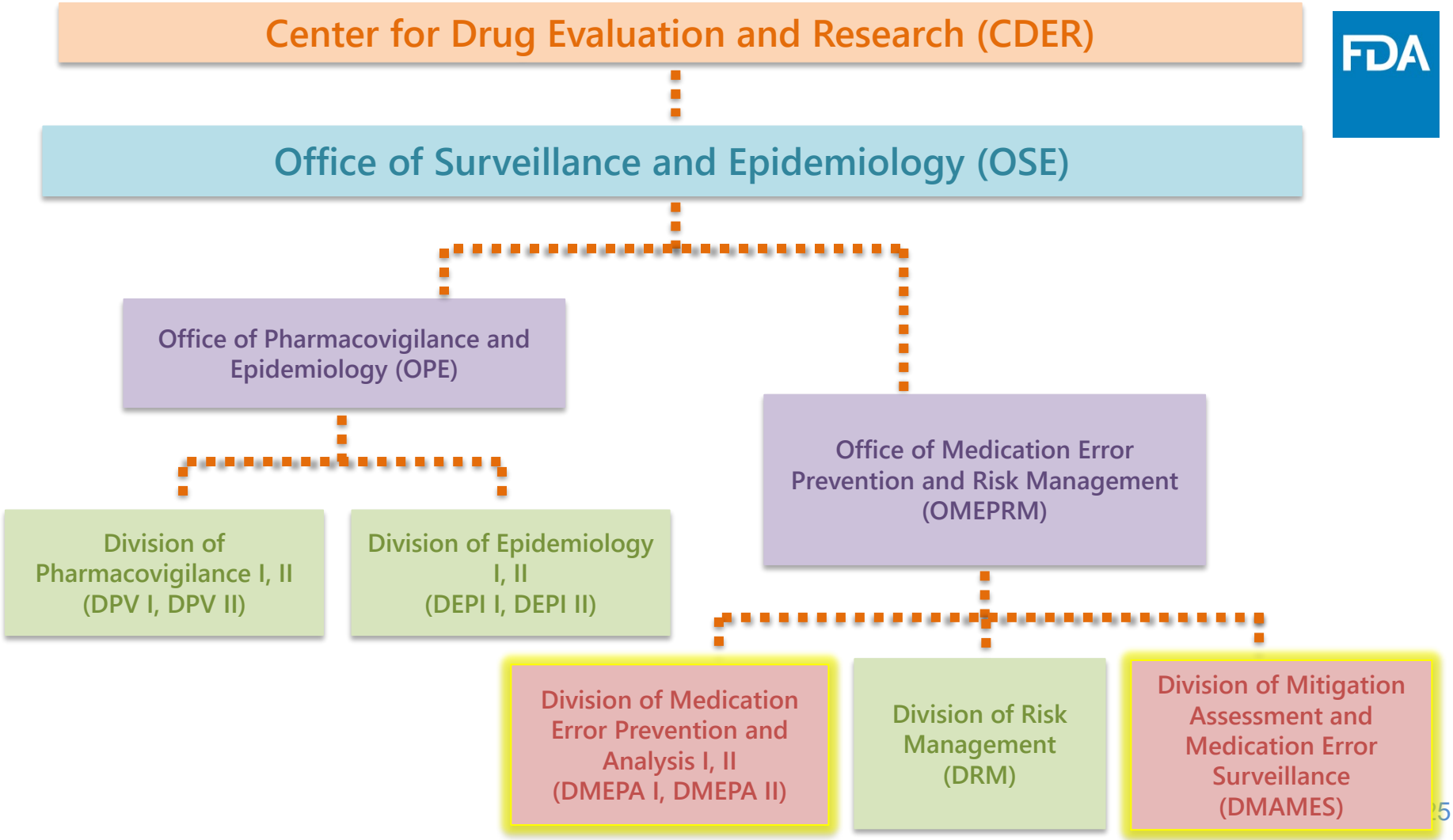
- **SLC**: Approve the updated labeling, which will be posted on Drugs@FDA and may be disseminated through other resources.
- **REMS**: Approve the proposed REMS for implementation.
- **PMR**: FDA will review the final study report to determine whether the requirement has been fulfilled or if other actions are necessary.

Naltrexone ER Injection Regulatory History - Key Actions Related to Postmarket Drug Safety



Post-approval Medication Error Surveillance




Center for Drug Evaluation and Research (CDER)
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Division of Pharmacovigilance I, II (DPV I, DPV II)
Division of Epidemiology I, II (DEPI I, DEPI II)
Division of Medication Error Prevention and Analysis I, II (DMEPA I, DMEPA II)
Division of Risk Management (DRM)
Division of Mitigation Assessment and Medication Error Surveillance (DMAMES)

Overview of OSE's Medication Error Prevention and Surveillance

Division of Medication Error Prevention and Analysis I and II (DMEPA I and DMEPA II)

- CDER Lead for **premarket** medication error prevention and analysis for drug and therapeutic biological products
- Evaluates weekly surveillance reports of medication errors submitted to the FDA Adverse Event Reporting System

Division of Mitigation Assessment and Medication Error Surveillance (DMAMES)

- CDER lead for **postmarket** medication error pharmacovigilance, including signal management
- CDER lead for assessing the effectiveness of risk evaluation and mitigation strategies (REMS) for drug products.
- Postmarket research and innovation

Both DMEPA and DMAMES consist of scientists and healthcare professionals with varied backgrounds

OSE: Office of Surveillance and Epidemiology
CDER: Center for Drug Evaluation and Research

Why is postmarket surveillance necessary?

- Limitations of premarket clinical trials
  - Trials are conducted under controlled conditions, and may not use the final approved name, labels, labeling, and packaging
  - Numbers of patients tested is too small to detect serious but rare problems, and some errors may fall into this category
  - Trials are often of short duration
- FDA has a robust program to identify potential errors and address them prior to approval. However, medications errors remain a significant burden on public health (NEHI, 2011)
- Allows us to monitor error reports and address the causes of errors that may be related to a drug's name, label, labeling, packaging, or product design

FDA Adverse Event Reporting System (FAERS) & Medication Error Reporting

- The FDA Adverse Event Reporting System (FAERS) is FDA's primary source for monitoring medication errors, but we surveil other sources as well.
  - Reporting of medication errors to FAERS is voluntary
- Depending on the type of error, root cause, contributing factors, and safety risks for a reported medication error, FDA may take regulatory action such as revising the labeling or issuing a safety communication to help prevent errors.
- In some cases, FDA may consider a change to the proprietary name to address safety issues resulting from name confusion errors.

DMEPA/DMAMES Surveillance Activities

- Screen medication error reports for potential safety signals
- Evaluate safety signals and perform risk assessment to determine if regulatory action is required
- Collaborate with other federal partners, other international regulators, researchers, and patient safety organizations
- Develop or review regulations, guidance, policies, and standards related to postmarketing surveillance
- Provide education and conduct research to better understand the causes of medication errors
- Inform our premarket review process based on what we learn postmarket

Naltrexone Extended-Release Injection

- Administered by healthcare provider
- Supplied in a carton containing:
  - one 380 mg vial naltrexone extended-release microspheres in a 5 mL single-dose vial,
  - one vial containing 4 mL of diluent (to deliver 3.4 mL) for the suspension
  - one 5-mL prepackaged syringe,
  - one 20-gauge 1-inch needle,
  - two 20-gauge 1 1/2-inch needles with needle protection devices, and;
  - two 20-gauge 2-inch needles with needle protection devices
- Intended route and site of administration
  - Via deep intramuscular – gluteal injection

Identification of Naltrexone Extended-Release Injection Safety Signal

- Between January 1, 2020, and May 1, 2021, we received 102* US reports in FAERS that described:
  - incorrect route of administration (n = 31 reports)
  - inappropriate site of injection (n = 72 reports)
  - administration by a family member or caregiver (n = 3 reports)
- Reported Outcomes
  - Hospitalizations (n = 5)
  - Life-threatening (n = 1)
  - Disability (n = 1)
  - Other serious (n = 10)

* One case described both incorrect route of administration and inappropriate site of product administration

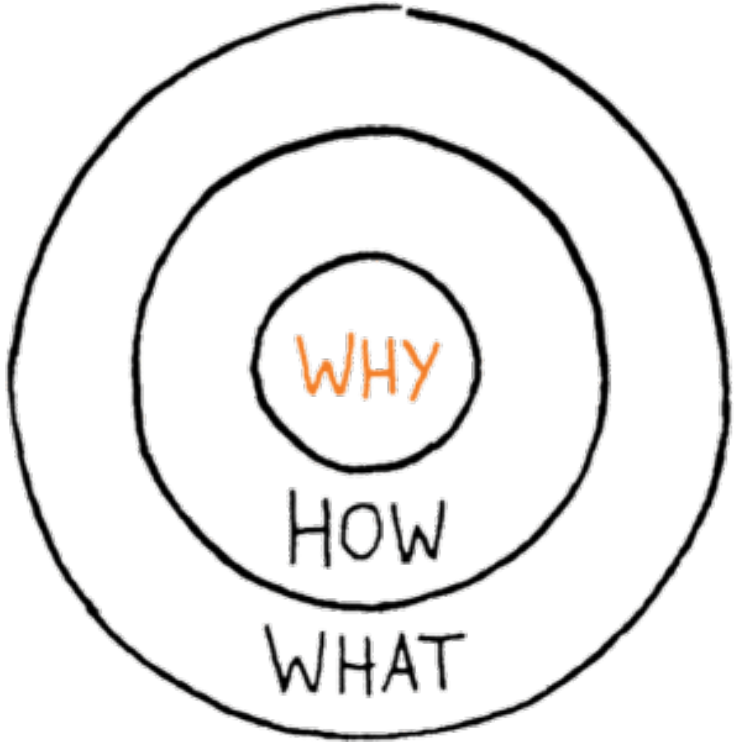
Challenge Question

What medication errors occurred that caused FDA to update labeling for naltrexone injection?

A. Wrong dose
B. Wrong site of administration
C. Wrong route of administration
D. B & C
E. All of the above

Root Cause Analysis (RCA) for Medication Errors

- A *tool* for identifying prevention strategies.
- Performed *retro*spectively, after an event (i.e., medication error) has occurred.
- The goal is to find out:
  - *What happened?*
  - *Why did it happen?*
  - *What to do to prevent it from happening again?*



This Photo by Unknown Author is licensed under CC BY-SA

RCA - Why did it happen?

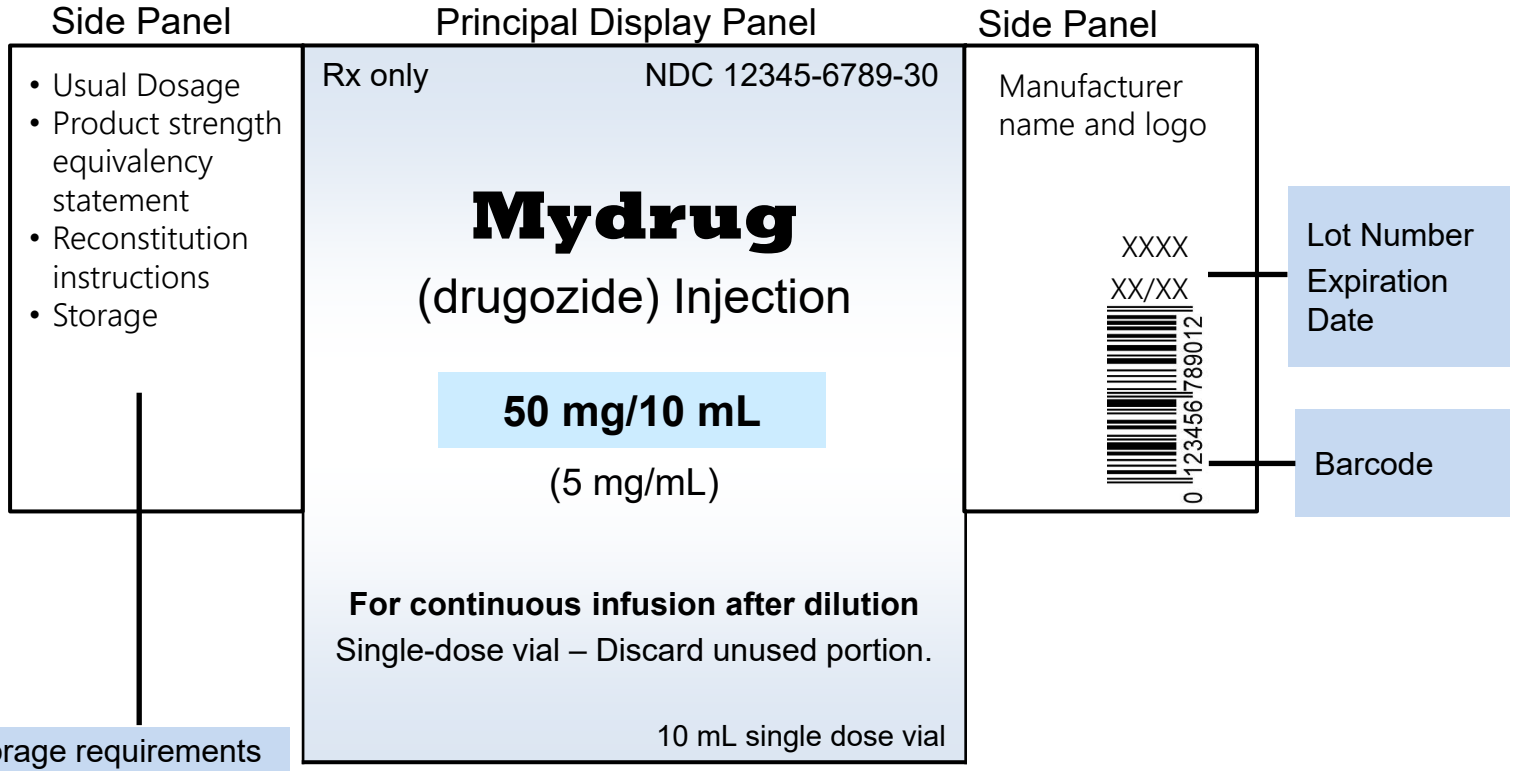
Contributing factors obtained from FAERS reports

- User new to the product
- Administered by family or caregiver
- Patient given option to receive injection in the arm
- Patient preferred to receive injection in the arm (deltoid)
- Did not use needle from the kit
- Off label use
- Wrong needle size
- Cachectic patient
- Some reports did not report a root cause/contributing factor, or it was inconclusive

Incorrect route of administration

Inappropriate site of injection

Product Information on Container Labels and Carton Labeling



(U.S. FDA, 2022)

Naltrexone Extended-Release Injection
New Safety Information

New Safety Information:
"…A **serious risk or an unexpected serious risk associated with use of the drug** that [FDA] has become aware of since the drug was approved, since the risk evaluation and mitigation strategy (REMS) was required, or since the last assessment of the approved [REMS] for the drug…"

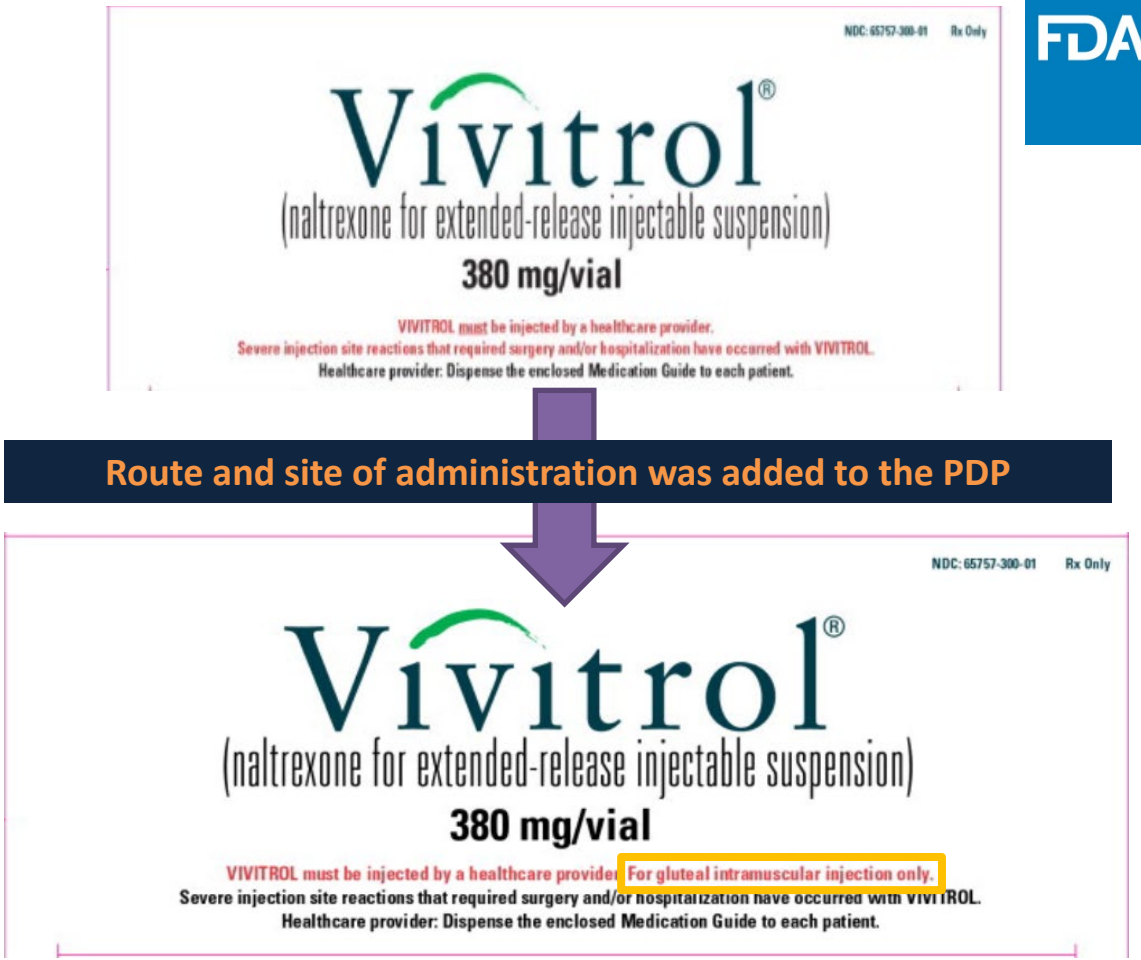
Section 505(o)(4) of the FDCA:

Require applicants to make **safety labeling changes**

Revisions recommended and implemented to address reported medication errors for the naltrexone extended-release injection labels and labeling

Safety Labeling Change:

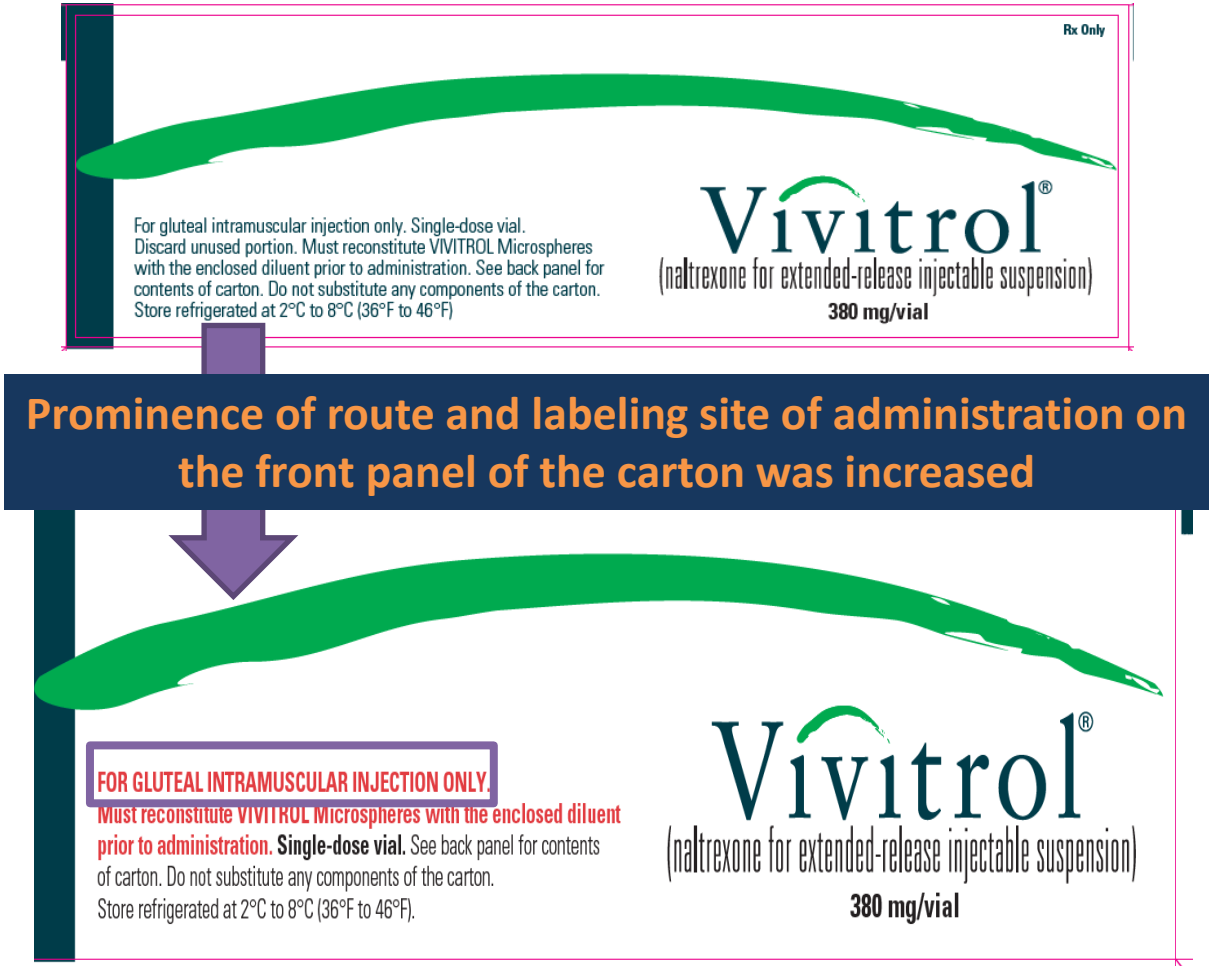
Vivitrol Carton Labeling Top Panel Principal Display



(https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cd11c435-b0f0-4bb9-ae78-60f101f3703f)

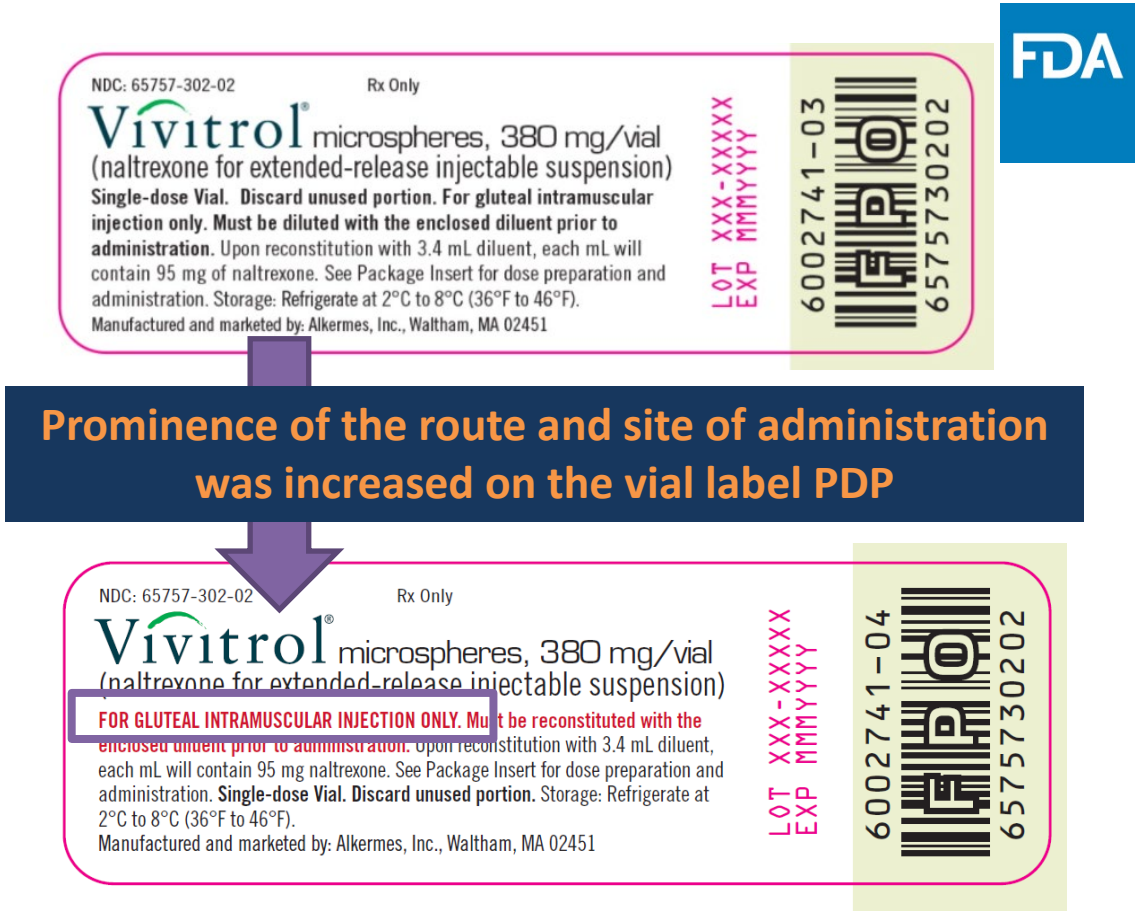
Safety Labeling Change:

Vivitrol Carton Labeling Front Panel Display



(https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cd11c435-b0f0-4bb9-ae78-60f101f3703f)

Safety Labeling Change:
Vivitrol Container Label



https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=cd11c435-b0f0-4bb9-ae78-60f101f3703f

Vivitrol Prescribing Information *(Prior to 2022 Labeling Update)** Section 2 Dosage and Administration

2. DOSAGE AND ADMINISTRATION

2.1. Important Dosage and Administration Information

VIVITROL must be prepared and administered by a healthcare provider.

Parenteral products should be visually inspected for particulate matter and discoloration prior to administration whenever solution and container permit. A properly mixed suspension will be milky white, will not contain clumps, and will move freely down the wall of the vial *[see Dosage and Administration (2.6)]*.

Prior to initiating VIVITROL, an opioid-free duration of a minimum of 7–10 days is recommended for patients, to avoid precipitation of opioid withdrawal that may be severe enough to require hospitalization *[see Warnings and Precautions (5.3)]*.

The recommended dose of VIVITROL is 380 mg delivered intramuscularly every 4 weeks or once a month. The injection should be administered by a healthcare provider as an intramuscular (IM) gluteal injection, alternating buttocks for each subsequent injection, using the carton components provided *[see How Supplied/Storage and Handling (16)]*. The needles provided in the carton are customized needles. VIVITROL must not be injected using any other needle. The needle lengths (either 1 1/2 or 2 inches) may not be adequate in every patient because of body habitus. Body habitus should be assessed prior to each injection for each patient to assure that needle length is adequate for intramuscular administration. For patients with a larger amount of subcutaneous tissue overlying the gluteal muscle, the administering healthcare provider may utilize the supplied 2-inch needle with needle protection device to help ensure that the injectate reaches the intramuscular mass. For very lean patients, the 1 1/2-inch needle may be appropriate to prevent the needle contacting the periosteum. Either needle may be used for patients with average body habitus. Healthcare providers should ensure that the VIVITROL injection is given

Site of injection (gluteal) was separated from dosage statement/route of administration

*This represents the previous version of the Prescribing Information for Vivitrol prior to the 2022 labeling update. (https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/021897s052lbl.pdf, 2021)

Safety Labeling Change:

Full Prescribing Information – Section 2 Dosage and Administration

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information

VIVITROL must be prepared and administered by a healthcare provider.

VIVITROL must ONLY be administered as a deep intramuscular gluteal injection.

Parenteral pr… administratio… milky white, … *and Administration (2.6)]*.

Prior … reco… enough to require hospitalization *[see Warnings and Precautions (5.3)]*.

The recommended dose of VIVITROL is 380 mg delivered intramuscularly (deep) as a gluteal injection every 4 weeks or once a month, alternating buttocks for each subsequent injection, using the carton components prov… needles provided in the carton are… any other needle. The needle leng… patient because of body habitus. E… patient to assure that needle lengt… with a larger amount of subcutane… healthcare provider may utilize th… ensure that the injectate reaches t… needle may be appropriate to prev… used for patients with average bo… VIVITROL injection is given cor…

2.6 Directions for Use

VIVITROL must be prepared and administered by a healthcare provider.

VIVITROL must ONLY be administered as a deep intramuscular gluteal injection.
To ensure proper dosing, it is important that you follow the preparation and administration

…must be administered only with one of the administration needles supplied in the carton. The …been provided to accommodate varying patient body habitus. For patients with a larger amount of subcutaneous tissue overlying the gluteal muscle, the administering healthcare provider may utilize the supplied 2-inch needle with needle protection device to help ensure that the injectate reaches the intramuscular mass. For very lean patients, the 1 1/2-inch needle may be appropriate …for patients with …l in case of clogging …components for the …5 minutes). …iscoloration prior to …uspension will be …f the vial *[see*

VIVITROL must ONLY be administered as a deep intramuscular gluteal injection.

The recommended dose of VIVITROL is 380 mg delivered intramuscularly (deep) as a gluteal injection…

Route and site of administration statement added to the beginning of:

- Section 2.1 Important Dosage and Administration Information
- Section 2.6 Directions for Use

Site of administration added to the recommended dosage statement:

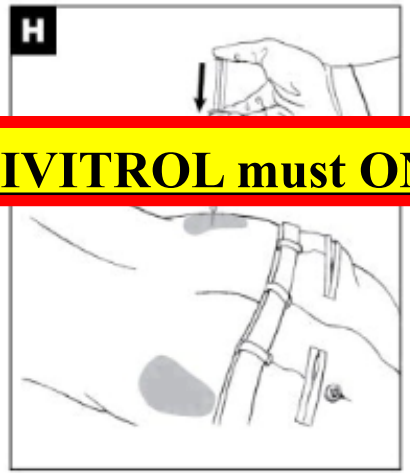
- Section 2.1 Important Dosage and Administration Information

(https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/021897s057lbl.pdf, 2022)

Safety Labeling Change:

Full Prescribing Information - 2 Dosage and Administration:

2.6 Directions for Use



1. Using a circular motion, clean the injection site with the alcohol swab. Let the site dry before injecting. Do not touch the site again before giving injections.

VIVITROL must ONLY be administered as a deep intramuscular gluteal injection.

monthly injection. Remember to aspirate for blood before injection. (see FIGURE H)

3. If blood aspirates or the needle clogs, do not inject. Change to the spare needle provided in the carton and administer into an adjacent site in the same gluteal region, again aspirating for blood before injection.
4. Inject the suspension in a smooth and continuous motion.

VIVITROL must ONLY be administered as a deep intramuscular gluteal injection.

Route and site of administration statement added with underlined text

(https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/021897s057lbl.pdf, 2022)

Full Prescribing Information – **5** Warnings and Precautions

5 WARNINGS AND PRECAUTIONS

5.1 Vulnerability to Opioid Overdose
5.2 Injection Site Reactions
5.3 Precipitation of Opioid Withdrawal
5.4 Hepatotoxicity
5.5 Depression and Suicidality
5.6 When Reversal of VIVITROL Blockade Is Required for Pain Management
5.7 Eosinophilic Pneumonia
5.8 Hypersensitivity Reactions Including Anaphylaxis
5.9 Intramuscular Injections
5.10 Alcohol Withdrawal
5.11 Interference with Laboratory Tests

(https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/021897s057lbl.pdf, 2022)

Full Prescribing Information –
5 Warnings and Precautions - 5.2 Injection Site Reactions

5.2 Injection Site Reactions

VIVITROL must be prepared and administered by a healthcare provider.

VIVITROL must ONLY be administered as a deep intramuscular gluteal injection.

VIVITROL injections may be followed by pain, tenderness, induration, swelling, erythema, bruising, or pruritus; however, in some cases injection site reactions may be very severe. In the clinical trials, one patient developed an area of induration that continued to enlarge after
4 weeks, with subsequent development of necrotic tissue that required surgical excision. In the postmarketing period, additional cases of injection site reaction with features including induration, cellulitis, hematoma, abscess, sterile abscess, and necrosis, have been reported. Some cases required surgical intervention, including debridement of necrotic tissue. Some cases resulted in significant scarring. The reported cases occurred primarily in female patients.

VIVITROL is administered as a deep intramuscular gluteal injection, and inadvertent subcutaneous injection of VIVITROL may increase the likelihood of severe injection site reactions. The needles provided in the carton are customized needles. VIVITROL must not be injected using any other needle. The needle lengths (either 1 1/2 or 2 inches) may not be adequate in every patient because of body habitus. Body habitus should be assessed prior to each injection for each patient to assure that the proper needle is selected and that the needle length is adequate for intramuscular administration. For patients with a larger amount of subcutaneous tissue overlying the gluteal muscle, the administering healthcare provider may utilize the supplied 2-inch needle with needle protection device to help ensure that the injectate reaches the intramuscular mass. For very lean patients, the 1 1/2-inch needle may be appropriate to prevent the needle contacting the periosteum. Either needle may be used for patients with average body habitus. Healthcare providers should ensure that the VIVITROL injection is given correctly, and should consider alternate treatment for those patients whose body habitus precludes an intramuscular gluteal injection with one of the provided needles.

Patients should be informed that any concerning injection site reactions should be brought to the attention of the healthcare provider *[see Patient Counseling Information (17)]*. Patients exhibiting signs of abscess, cellulitis, necrosis, or extensive swelling should be evaluated by a physician to determine if referral to a surgeon is warranted.

Key Points to Highlight

VIVITROL must ONLY be administered as a deep intramuscular gluteal injection.

- Healthcare providers should ensure that the VIVITROL injection is given correctly and should consider alternate treatment for those patients whose body habitus precludes an intramuscular gluteal injection with one of the provided needles.
- Patients should be informed that any concerning injection site reactions should be brought to the attention of the healthcare provider *[see Patient Counseling Information (17)]*.
- Patients exhibiting signs of abscess, cellulitis, necrosis, or extensive swelling should be evaluated by a physician to determine if referral to a surgeon is warranted.

Challenge Question

What is the correct site and route of administration for naltrexone extended-release injection?

A. Subcutaneous, upper arm or stomach
B. Intramuscular, thigh
C. Deep intramuscular, gluteal

Full Prescribing Information – 17 Patient Counseling Information

17 Patient Counseling Information

Advise the patient to read the FDA-Approved patient labeling (Medication Guide).

Physicians should include the following issues in discussions with patients for whom they prescribe VIVITROL.

…

VIVITROL for All Indications:

- Inform patients on VIVITROL that they may not experience the expected effects from opioid-containing analgesic, antidiarrheal, or antitussive medications.
- Instruct patients that VIVITROL must be prepared and administered by a healthcare provider.
- Advise patients that a reaction at the site of VIVITROL injection may occur. Reactions include pain, tenderness, induration, swelling, erythema, bruising, or pruritus. Serious injection site reactions including necrosis may occur. Some of these injection site reactions have required surgery. Patients should be advised to seek medical attention for worsening skin reactions.

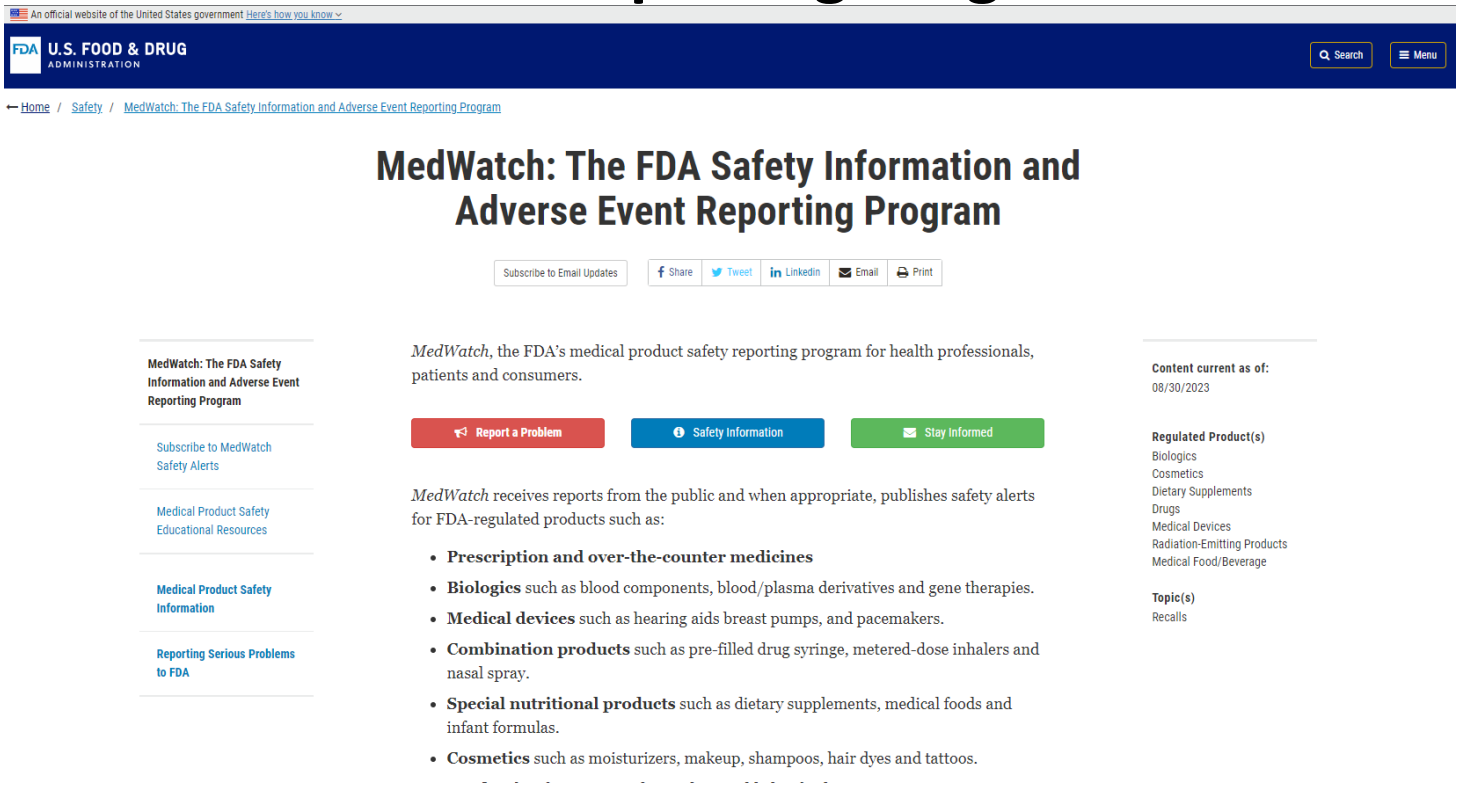
…

Key Points to Highlight

Advise patients that a reaction at the site of VIVITROL injection may occur. Reactions include pain, tenderness, induration, swelling, erythema, bruising, or pruritus. Serious injection site reactions including necrosis may occur. Some of these injection site reactions have required surgery. Patients should be advised to seek medical attention for worsening skin reactions.

(https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/021897s057lbl.pdf, 2022)

Medwatch – FDA's Medical Product Safety Reporting Program



(https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program, 2024)

Key Takeaways:
How healthcare providers can contribute to postmarketing drug safety within their practice

Read Full Prescribing Information	Use Proper Injection Techniques	Educate Patients on Medication Risks	Report Adverse Events to MedWatch
Before administering naltrexone extended-release injection, thoroughly read and understand the Full Prescribing Information, especially regarding proper preparation and injection technique.	Only healthcare providers should administer the product. Ensure naltrexone extended-release injection is prepared correctly and administered using proper injection technique at the correct site and route of administration.	Counsel patients on the signs and symptoms of injection site reactions and when to notify their healthcare provider.	Report any observed or suspected adverse events for medical products to FDA through Medwatch.

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Healthcare Provider Resources

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Q and A

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- CDR Mark A. Liberatore, PharmD, RAC; Deputy Director for Safety
- CDR Jessica Voqui, PharmD, MS, RAC; Associate Director for Postmarket Regulatory Science

Division of Medication Error Prevention and Analysis 1 (OSE/OMEPRM)

- LCDR Valerie S. Vaughan, PharmD; Team Leader
- Sofanit Getahun, PharmD, BCPS; Safety Evaluator

How to Obtain CE/CME Credits

2024 MAY CCSS: Bridging Gaps and Building Resilience in Primary Care

Complete the course evaluation and posttest for the session(s) you attended by **11:59 PM ET on Thursday, May 23, 2024**, to receive CE/CME credit or a certificate of attendance.

1. Log in to your account.
2. Go to the main event page and select the session you want to complete under the TAKE COURSE tab.
3. On the session page, click TAKE COURSE under the TAKE COURSE tab.
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Questions? Email DHA J7, CEPO at dha.ncr.j7.mbx.cepo-cms-support@health.mil.


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