

Prescriber Education: FDA REMS Options and Considerations

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**Training Health Care Providers on Pain
Management and Safe Use of Opioid Analgesics-
Exploring the Path Forward; Public Workshop
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Purpose

Provide examples of how the FDA REMS authorities are used to ensure prescriber training, how this could be accomplished for opioid analgesic prescribers, and the potential impact of such a program

Outline

- REMS Background
- Overview of current Risk Evaluation and Mitigation Strategies (REMS) and prescriber training options
- Restrictive REMS: Operation, participation and examples
- Possible Opioid Analgesic REMS operations and stakeholder impact
- Considerations

REMS Background

- A REMS is a required risk management plan that utilizes risk mitigation strategies beyond FDA-approved professional labeling
- Food and Drug Administration Amendments Act of 2007 provided FDA the legal authority to require a REMS for applicable drugs*
 - Pre-approval, if FDA determines a REMS is needed to ensure the benefits of the drug outweigh the risks
 - Post-approval, if FDA becomes aware of new safety information and determines that a REMS is necessary
- REMS are developed and implemented by the drug manufacturers

* Section 505-1 of Food, Drug, and Cosmetic Act (FDCA)

Components of a REMS

- A REMS can include
 - Medication Guide or Patient Package Insert (PPI)
 - Communication Plan for Health care Providers (HCPs)*
 - Elements to Assure Safe Use
 - Implementation System
- Must include a Timetable for Submission of Assessments of the REMS*

**Note: This requirement applies to NDAs and BLAs only.*

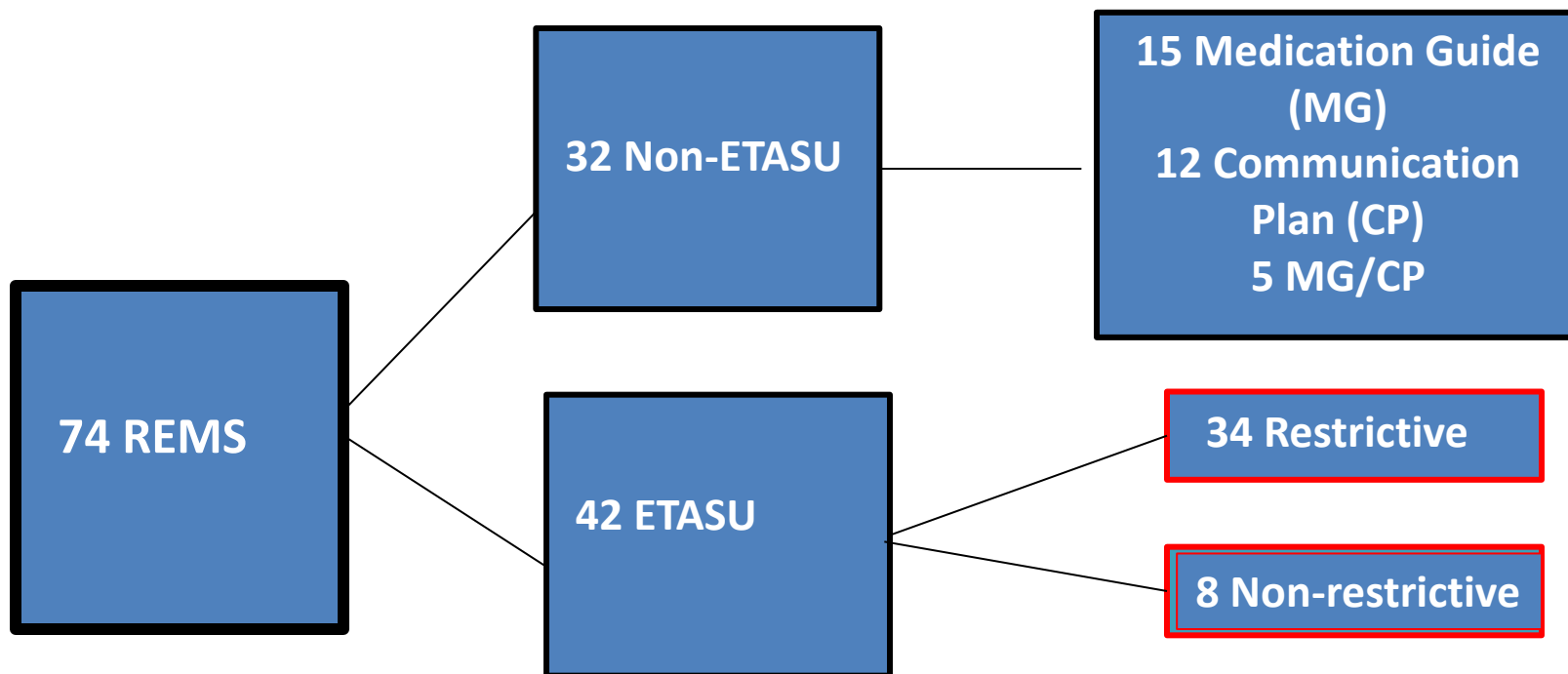


Elements to Assure Safe Use (ETASU)



- **Certification and/or specialized training of health care providers who prescribe the drug(s)**
- **Certification of pharmacies or other dispensers of the drug**
- Dispensing/administration of drug in certain health care settings e.g., hospitals
- Drug is dispensed/administer only with evidence of safe use conditions
- Each patient using the drug is subject to certain monitoring
- Enrollment of treated patients in registries

Current REMS



Prescriber training options: ETASU REMS

Restrictive

Components of a REMS are linked to distribution/dispensing the drug

- certification/training of prescribers
- certification of pharmacies and/or healthcare settings
- documentation of safe use conditions

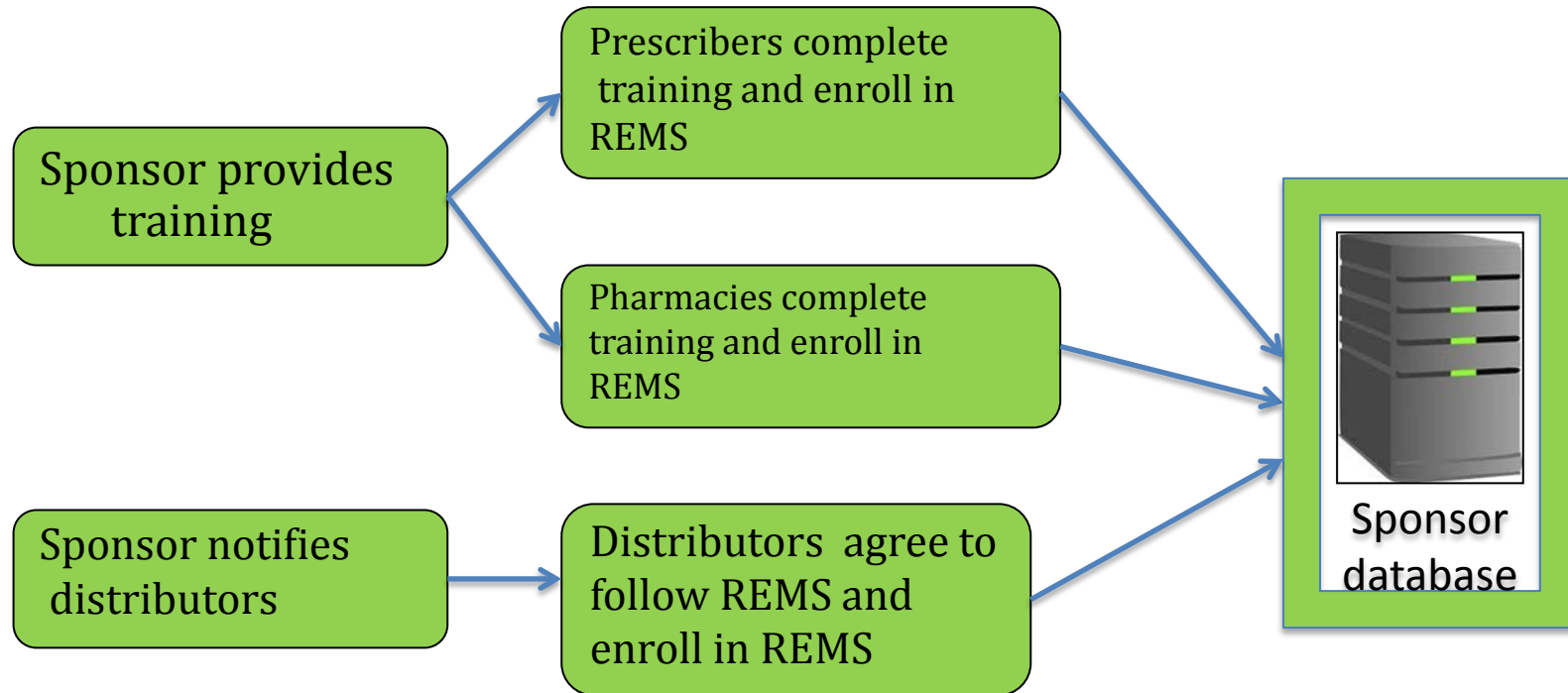
Non-restrictive

Components of a REMS are not linked to distribution/dispensing the drug

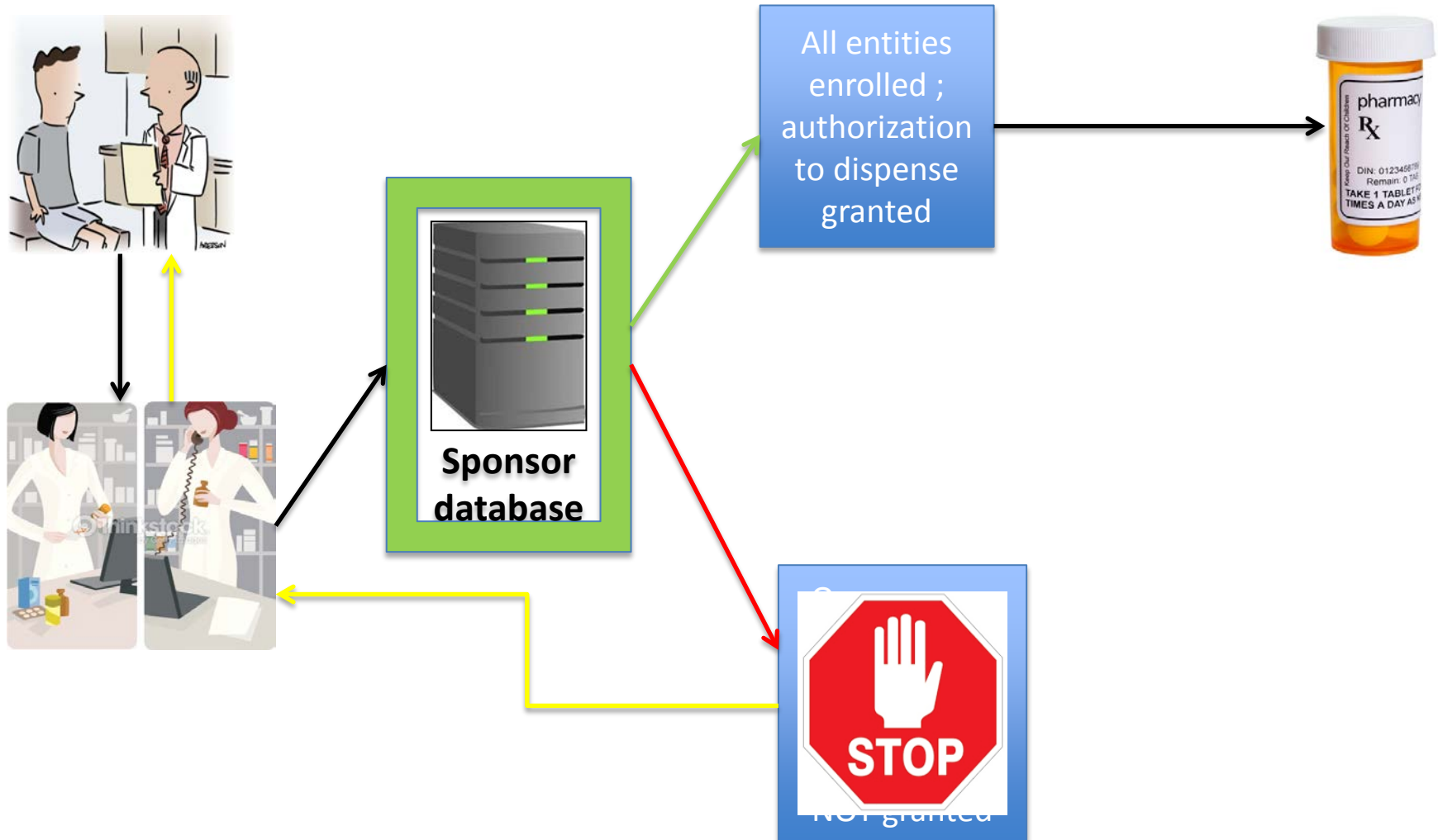
- manufacturers are required to make training available to likely prescribers

RESTRICTIVE REMS: OPERATIONS

Example: REMS restricts prescribing to trained prescribers

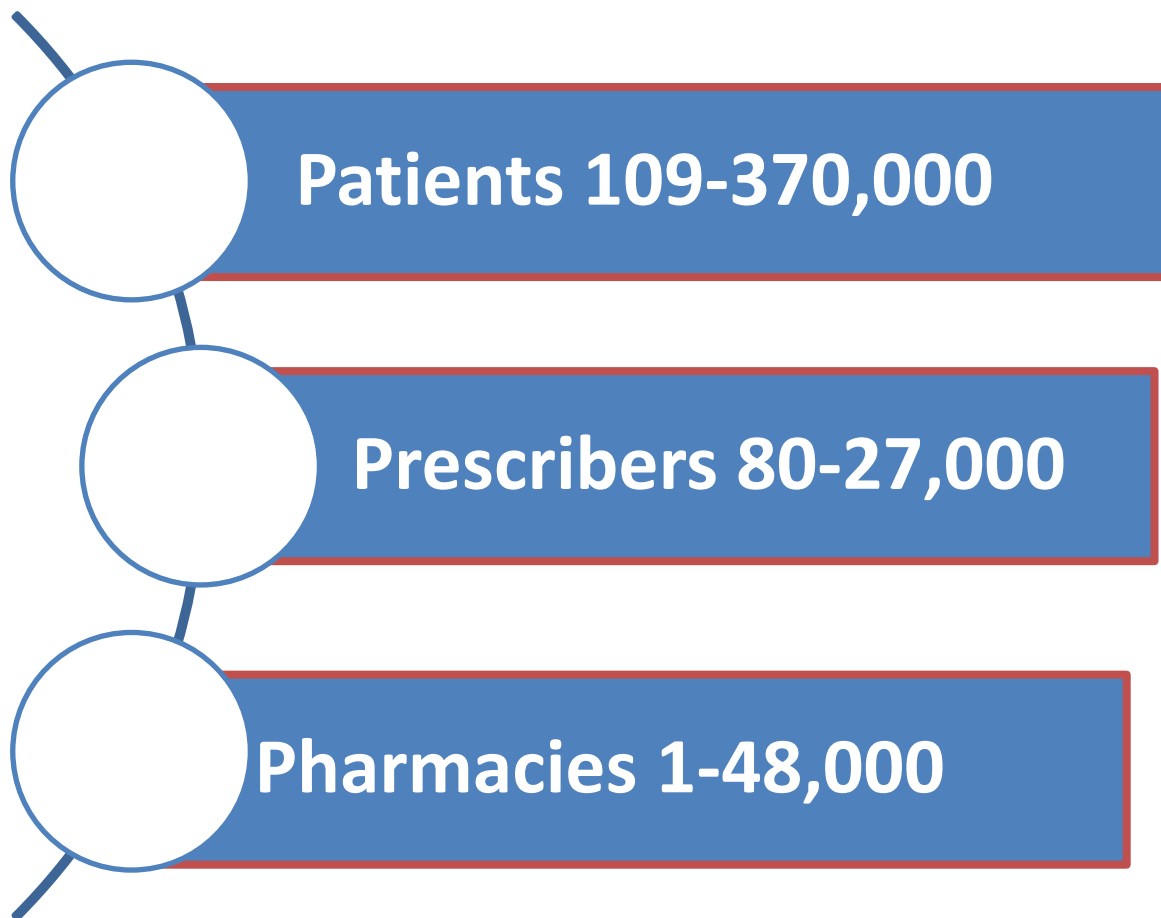


Example: REMS restricts prescribing to trained prescribers



RESTRICTIVE REMS: PARTICIPATION

Stakeholder participation in selected restrictive REMS



More than half of selected programs

- <10,000 patients
- <10,000 prescribers
- <10,000 pharmacies participating

*REMS assessment data from 16/34 programs with ETASU; prescriber and pharmacy enrollment required, at least two annual assessments

RESTRICTIVE REMS: EXAMPLES

Isotretinoin (iPLEDGE) REMS

- Shared-system REMS
 - Approved 2005
 - 5 application holders
- Indicated for severe recalcitrant nodular acne
- Risk of teratogenicity
- REMS goals
 - Prevent fetal exposure and inform prescribers, pharmacists and patients about the serious risks and safe use conditions

iPLEDGE REMS

stakeholder requirements

PRESCRIBER

- Reviews educational material and enrolls
- Counsels and completes informed consent (IC) with patient
- Enrolls patient by appropriate risk category
- Documents safe use conditions met each month for Females of Reproductive Potential

PHARMACY

- Reviews educational material and enrolls
- Provides patient with MedGuide
- Obtains and documents authorization to dispense
- Dispenses no more than 30 days supply

PATIENT

- All complete Informed Consent
- Females of reproductive potential:
 - Pre-treatment and monthly pregnancy tests required
 - Complete monthly comprehension questions required

Transmucosal Immediate-release fentanyl (TIRF) REMS



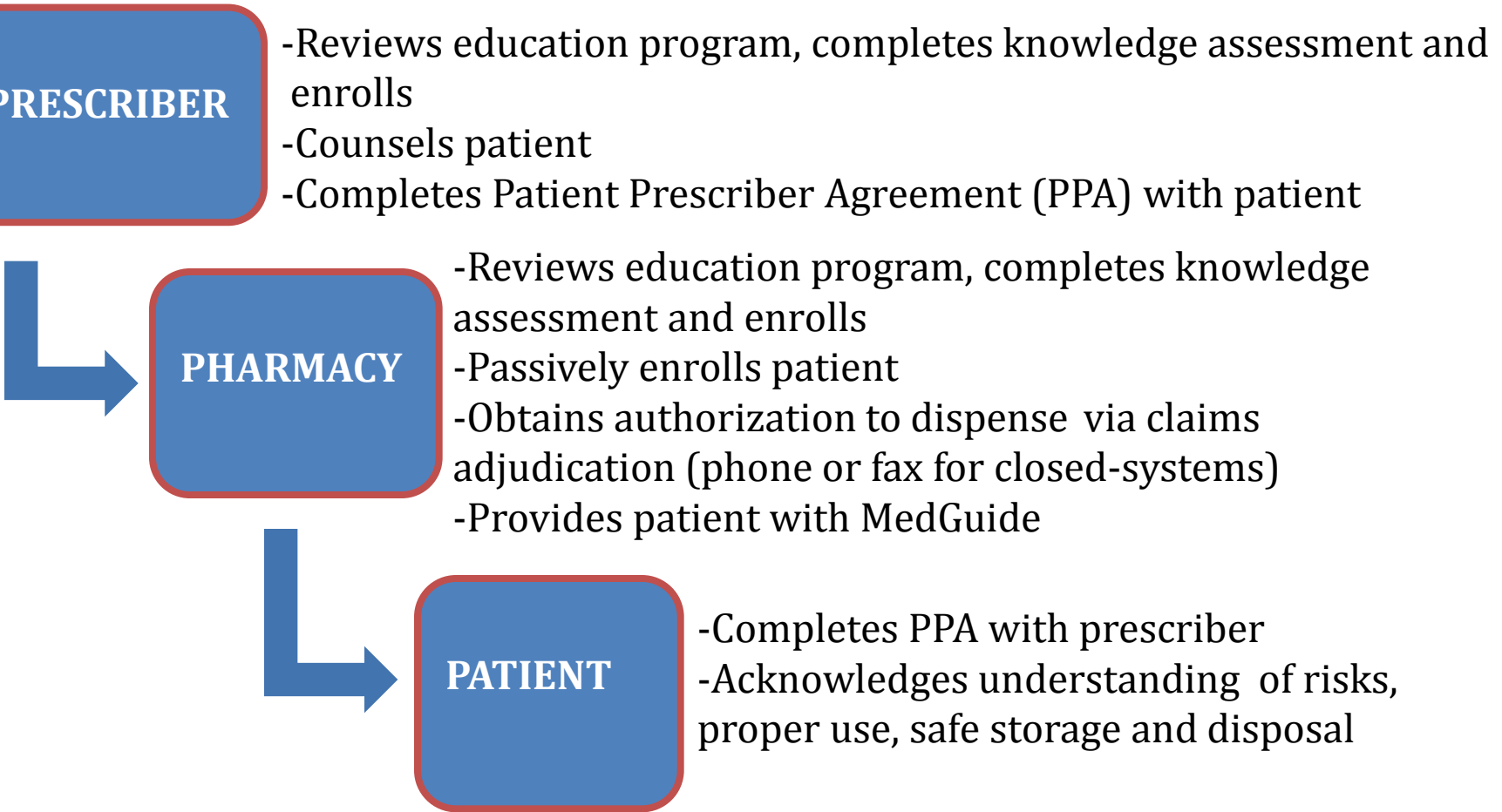
- Shared-system REMS
 - Approved December 2011
 - 8 application holders
- Product Information
 - Formulations include a buccal film, buccal tablet, sublingual spray, and nasal spray of fentanyl citrate
 - Indicated for breakthrough pain in cancer patients 18 years* of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain
- REMS Goal
 - Mitigate the risk of misuse, abuse, addiction, overdose and serious complications due to medication errors

*one TIRF indicated for age 16 years and older

TIRF REMS stakeholder requirements

PRESCRIBER

- Reviews education program, completes knowledge assessment and enrolls
- Counsels patient
- Completes Patient Prescriber Agreement (PPA) with patient



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graph TD; PRESCRIBER --> PHARMACY; PHARMACY --> PATIENT;
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PHARMACY

- Reviews education program, completes knowledge assessment and enrolls
- Passively enrolls patient
- Obtains authorization to dispense via claims adjudication (phone or fax for closed-systems)
- Provides patient with MedGuide

PATIENT

- Completes PPA with prescriber
- Acknowledges understanding of risks, proper use, safe storage and disposal

POSSIBLE OPIOID ANALGESIC REMS: OPERATIONS AND STAKEHOLDER IMPACT

Possible Opioid Analgesic REMS stakeholder requirements



PRESCRIBER

- Complete training and knowledge assessment and enroll in REMS

PHARMACY

- Complete training and knowledge assessment and enroll in REMS
- Obtain authorization to dispense
- Provide patient with MedGuide

PATIENT

- No specific patient requirements

Stakeholders impacted

REMS program	Active prescribers	Active pharmacies	Prescriptions dispensed	Patients
TIRF REMS ^a	8000	42,000	63,000 ^b	4200 ^c
iPLEDGE REMS ^a	16,000	48,000	1.3 million	370,000
	Possible Prescribers	Possible pharmacies	Possible prescriptions dispensed	Possible patients
Opioid analgesic REMS	1.5 million ^d	67,000	160 million ^e	±80 million ^f

a Most recent annual REMS assessment reviewed

b National Prescription Audit (NPA) and static data 2006-2011. January 2011-December 2016. Extracted April 2017

c Newly enrolled patients only 2016 REMS assessment data

d Current DEA provider and mid-level practitioner registrants, April 2017, extracted 5/2/17

<https://apps.deadiversion.usdoj.gov/webforms/odrRegSummaryReport.do?jsessionid=C7D39B31028E9E8F37043344DA286988>

e National Prescription Audit (NPA) and static data 2006 -2011. January 2011 -December 2016. Extracted April 2017.

f IMS Health Vector One®: Total Patient Tracker, 2002-2014. Hwang CS, Kang EM, Kornegay CJ, Staffa JA, Jones CM, McAninch JK. Trends in the concomitant prescribing of opioids and benzodiazepines, 2002-2014. *Am J Prev Med.* 2016;51(2):151-60.

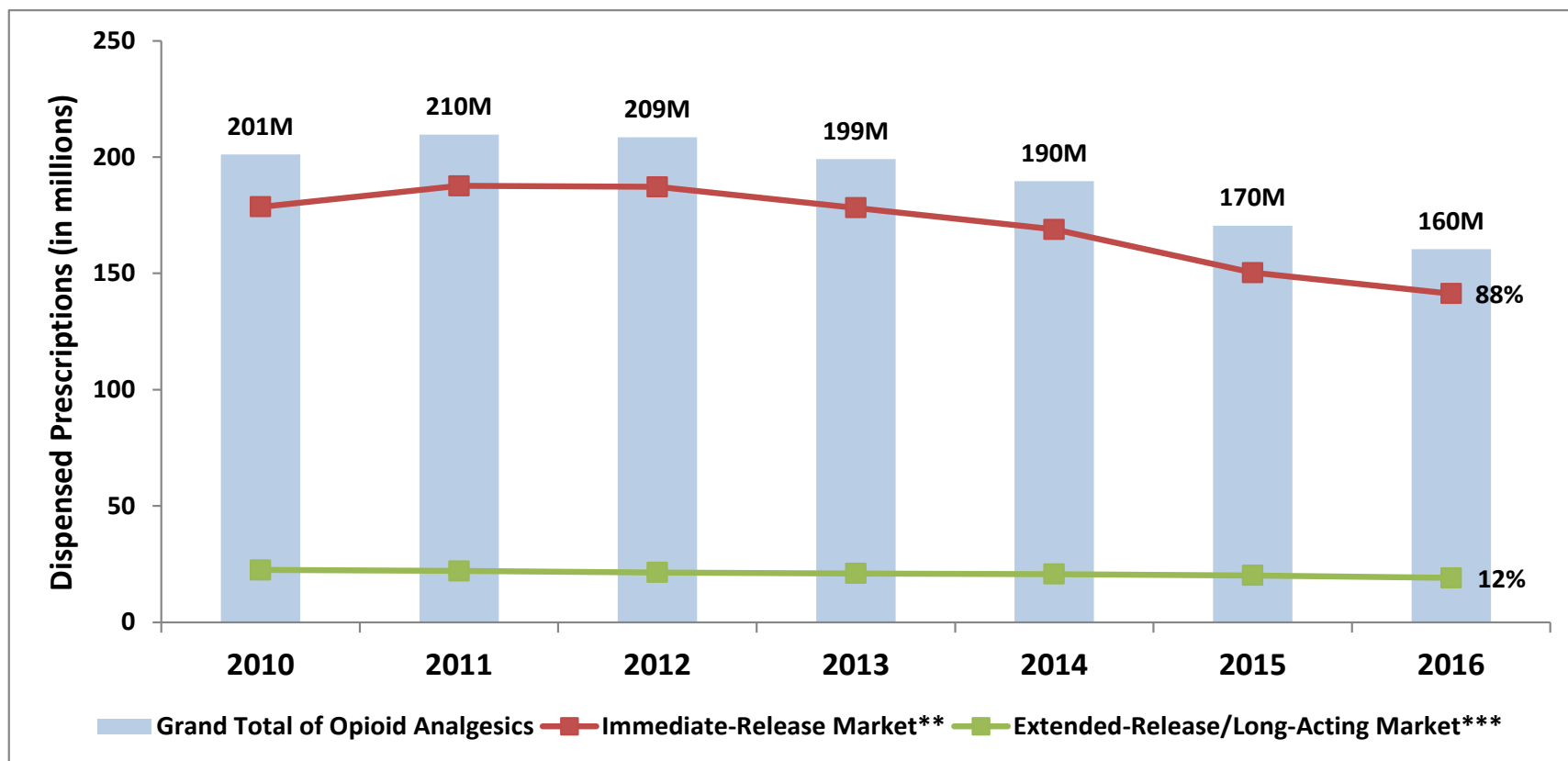
Considerations: Using FDA REMS authority to ensure training of prescribers



- May limit number of opioid analgesic prescribers and potentially impact patients
- Duplicative of existing requirements (e.g., states, healthcare systems)
- Requires separate, parallel registration of all DEA registered prescribers
- Number of prescribers required to enroll would be much greater than any current REMS
- Implementation, Operation, Maintenance and Evaluation controlled by Industry



Nationally Estimated Number of Prescriptions Dispensed for Opioid Analgesics* Products from U.S. Outpatient Retail Pharmacies



Source: National Prescription Audit (NPA) and static data 2006-2011. January 2010-December 2016. Extracted March 2017.

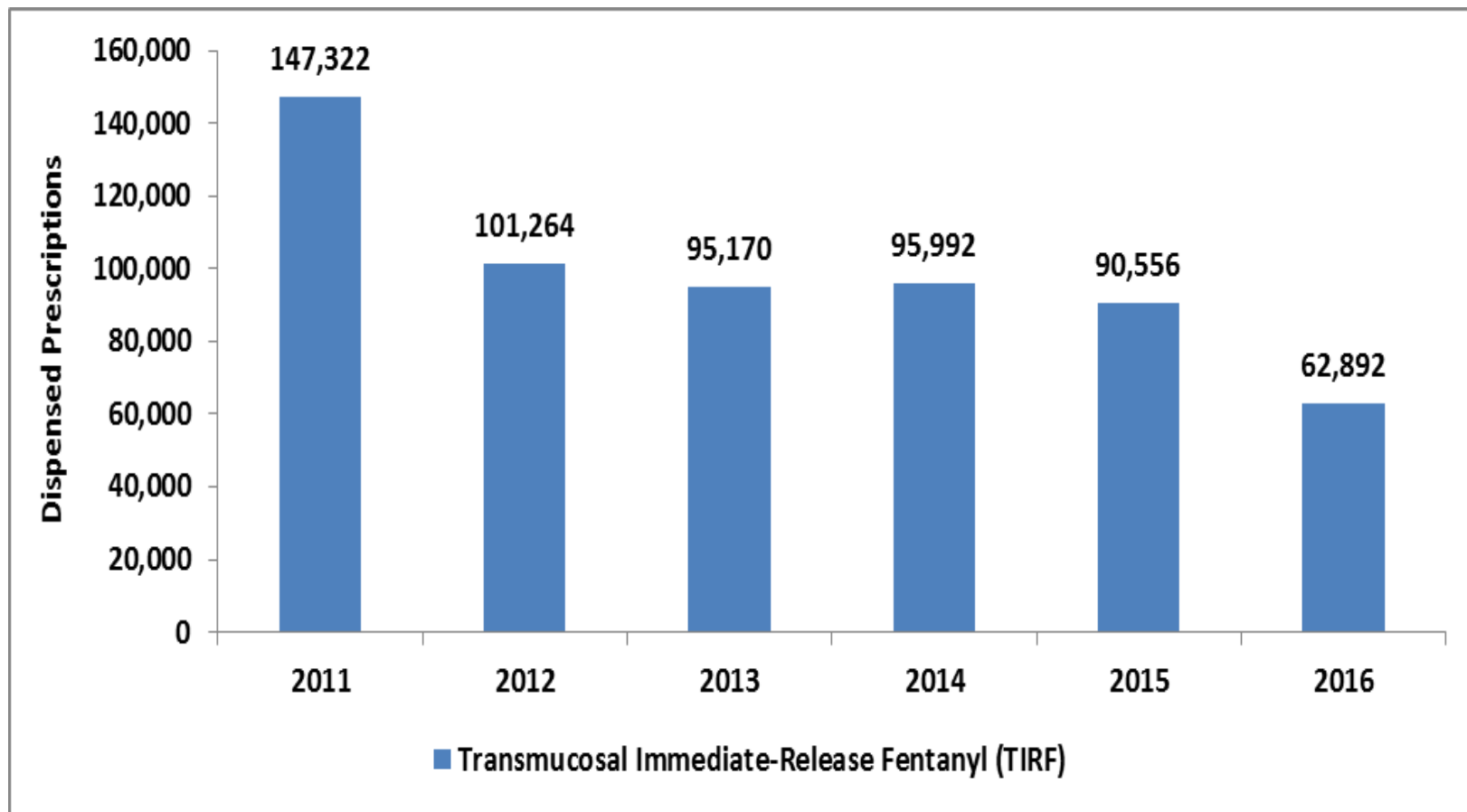
*Includes all schedule-II opioid analgesics only

**Immediate-Release formulations include oral solids, oral liquids, rectal, nasal.

***Extended-Release/Long-Acting formulations include oral solids and transdermal patches.

Note: Products include opioid analgesics only. Injectables, opioid-containing cough-cold products, and opioid-containing medication-assisted treatment (MAT) products were not included in this data.

Nationally Estimated Number of Prescriptions Dispensed for TIRF* Products from U.S. Outpatient Retail Pharmacies



Source: National Prescription Audit (NPA) and static data 2006-2011. January 2011-December 2016. Extracted April 2017.

*TIRFs include: Abstral, Actiq, Fentanyl Citrate (generic), Fentora, Lazanda, Onsolis, and Subsys

Schedule-II Opioid Analgesics

Extended-Release/Long-Acting Opioid Molecules include the following:

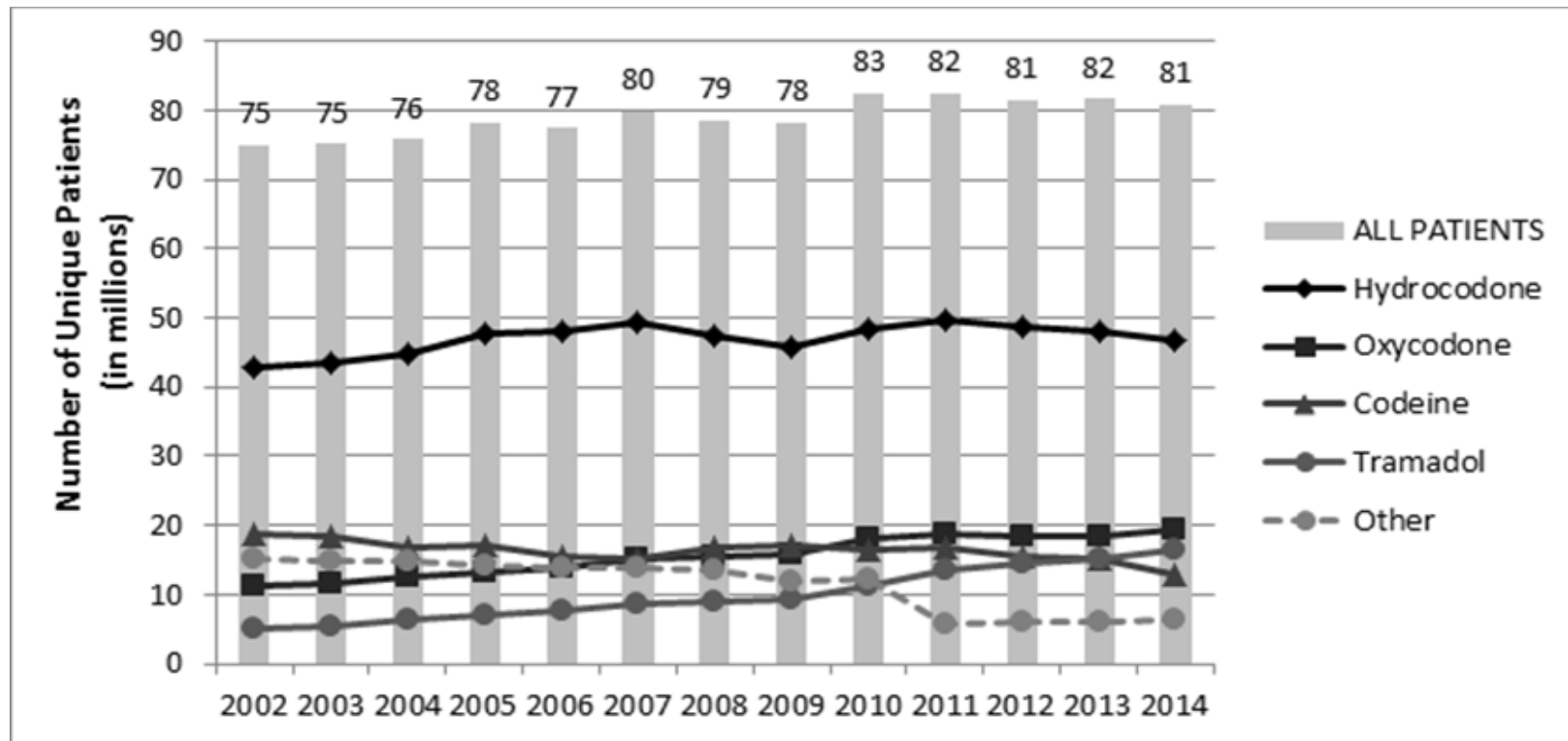
- Fentanyl Transdermal Patch
- Hydrocodone ER
- Hydromorphone ER
- Methadone
- Morphine ER
- Morphine/Naltrexone ER
- Oxycodone ER
- Oxycodone ER combination analgesic (oxycodone with acetaminophen, ibuprofen, or acetylsalicylic acid)
- Oxymorphone ER
- Tapentadol ER

Immediate-Release Opioid Molecules include the following:

- Codeine IR
- Fentanyl IR
- Hydrocodone IR combination analgesic (hydrocodone with acetaminophen, ibuprofen, or acetylsalicylic acid)
- Levorphanol IR
- Meperidine IR
- Meperidine/Promethazine IR
- Opium
- Oxycodone Single-Entity IR
- Oxycodone IR combination
- Oxymorphone IR
- Hydromorphone IR
- Morphine IR
- Tapentadol IR

Note: Products include opioid analgesics only. Injectable , opioid-containing cough-cold products, and opioid-containing medication-assisted treatment (MAT) products were not included in this data.

Nationally projected trends in the annual number of unique patients dispensed opioids in the U.S., 2002–2014



“Other” includes buprenorphine, butorphanol, dihydrocodeine, fentanyl, hydromorphone, levorphanol, meperidine, methadone, morphine, oxymorphone, pentazocine, propoxyphene, and tapentadol. Source: IMS Health Vector One®: Total Patient Tracker, 2002–2014