Abuse-Deterrent Formulations

Balancing Evidence with Value

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Disclosure Statement

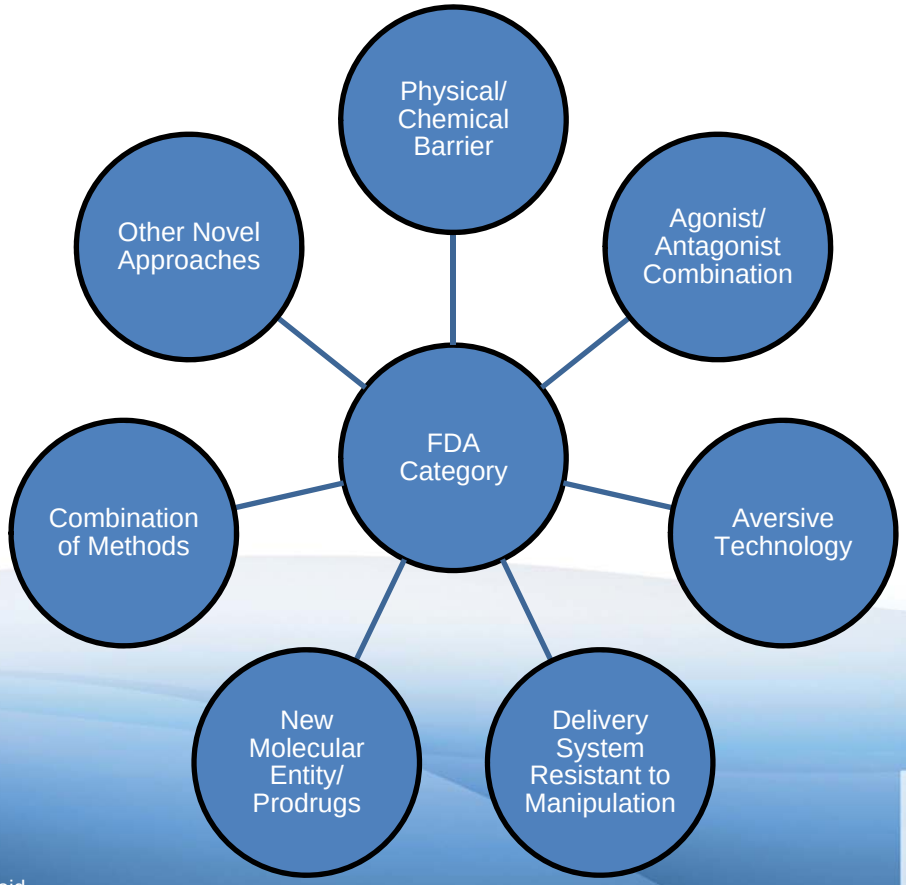
- I have no actual or potential conflict of interest in relation to this presentation

OBJECTIVES

- Review the concept of abuse-deterrent opioid formulations (ADFs)
- Discuss the types of studies that are required for a manufacturer to obtain abuse-deterrent labeling for a product
- Identify the ADFs that are currently approved and their mechanisms of abuse-deterrence
- Summarize the Evidence Report on ADFs prepared by the Institute of Clinical and Economic Review (ICER)
- Review states' activities related to ADFs

Abuse-Deterrent Opioid Formulation (ADF) Basics

- Formulated to meaningfully deter abuse of the opioid
- According to the Food and Drug Administration (FDA) ADFs may be categorized by the following methods:



ADF Premarket Studies

Study Category	Study Type	General Purpose
Category 1	*in vitro* manipulation and extraction studies	• Evaluate how difficult product is to tamper with • Discover what methods of tampering are possible
Category 2	Pharmacokinetic studies	• Compare *in vivo* pharmacokinetic properties of manipulated versus intact formulation
Category 3	Clinical abuse potential studies	• Assess abuse potential of intact and manipulated formulation • Multiple routes of administration may be investigated, if relevant.

In vitro Manipulation and Extraction Studies (Category 1)

- Ability to crush, cut, grate or grind tested
  - Common household items → coffee grinders, pill cutters, pedicure tools, etc.
  - Particle size from manipulation should be assessed
- Ability to dissolve in solvents
  - Can the product be drawn into a syringe for injection? How much?
- Ability to extract in solvents
  - Panel of solvents → water, vinegar, ethanol, acetone, organic solvents, etc.
  - Effects of time, temperature, pH and agitation upon extractability also tested
- If product is abused by smoking, smoking simulation study
  - Assess how much drug is released in vapor

Category 1 Study Example – oxycodone ER microspheres

- Study assessed ability to prepare manipulated and intact oxycodone ER microspheres for injection
- Microspheres added to 5 mL, 10 mL, and 15 mL water samples
  - Water at room temperature, 90° C, and 95° C
  - Agitation over 5, 15, and 30 minute periods
- Highest amount extracted 11.2% of oxycodone from manipulated microspheres under heated conditions in 10 mL water.
- Microspheres placed into suspension
  - Maximum of 13.6% of oxycodone in dosage form able to pass through an 18 G needle.
- Melting microspheres to draw into syringe resulted in solidification in needle almost instantly.

Category 1 Challenges

- Category 1 studies do not uncover all methods of defeating ADF mechanisms.
- Ways to defeat the ADF mechanisms are easily found online.
- This user describes using pliers to allow for crushing of OxyContin® (oxycodone ER)
- Other users describe the use of power tools and pedicure tools

Image source: http://www.bluelight.org/vb/threads/526671-How-to-Abuse-OP-OxyContin-How-to-Get-High-OP-OxyContin

Pharmacokinetic Studies (Category 2)

- Objective → Compare manipulated ADF to intact formulation
  - Also compared with intact formulations of comparator product(s)
- Most effective method of manipulation established in Category 1 to be used
- Multiple routes may be evaluated
- Typical pharmacokinetic endpoints evaluated
  - Maximum concentration (C_{max}), time to maximum concentration (T_{max}), terminal elimination half-life ($T_{1/2}$), etc.
- May be incorporated into Category 3, rather than stand-alone studies

Clinical Abuse Potential Studies (Category 3)

- Designed as R, DB, PC, PoC, XO studies
- Naloxone challenge → exclude opioid dependent subjects
- ADF compared to non-ADF of same active ingredient
- Typical endpoints include responses on visual analogue scales (VAS) for drug liking, willingness to take drug again, etc. or Profile of Mood States (POMS)
- FDA considers subjective VAS responses and POMS as predictive of the likelihood of abuse

DB=double blind, PC=placebo-controlled, PoC=positive-controlled, R=randomized, XO=crossover

Category 3 Study Example – ADF Morphine ER Tablet

- Intranasal (IN) abuse potential of crushed ADF MSER tablet compared to crushed non-ADF MSER tablet in 27 subjects
  - Placebo and intact oral ADF MSER also included for comparison
- Study design: R, DB, DD, PC, 4-way XO
- Primary endpoint: Maximum mean drug liking (E_{max}) on bipolar 100 mm VAS
- Results: IN ADF MSER E_{max} of 71.13 mm versus IN non-ADF MSER E_{max} of 84.79 mm (P<0.0001)
  - Bipolar scale → E_{max} of 0 = strong disliking, E_{max} of 50 = neither like nor dislike, E_{max} of 100 = strong liking
  - Result statistically significant – Clinically significant?

Quiz Question

A Category 3 study is always required to establish a claim of abuse-deterrence via the intravenous (IV) route:

A. True

B. False

Quiz Question – Answer

A Category 3 study is always required to establish a claim of abuse-deterrence via the intravenous (IV) route:

A. True

B. False – Category 1 studies may be sufficient to establish abuse-deterrence via the IV route for products with a physical/chemical barrier to manipulation

Currently Approved ADFs

Physical/Chemical Barrier to Manipulation	Agonist/Antagonist Combination
Arymo ER® (morphine extended-release)	Embeda® (morphine extended-release/naltrexone)
Hysingla ER® (hydrocodone extended-release)	Targiniq ER® (oxycodone extended-release/naloxone)*
MorphaBond ER® (morphine extended-release)	Troxyca ER® (oxycodone extended-release/naltrexone)*
OxyContin® (oxycodone extended-release)	
RoxyBond® (oxycodone immediate-release)*	
Vantrela ER® (hydrocodone extended-release)*	
Xtampza ER® (oxycodone extended-release)	

*FDA-approved, but not commercially available in the US as of 10/10/17

Physical/Chemical Barrier Example

- Original formulation of OxyContin® (oxycodone extended-release) was easily manipulated to reduce particle size substantially
- New formulation (ADF) of OxyContin® (oxycodone extended-release) presents a greater challenge in particle size reduction
- Larger particle size is more challenging to insufflate (snort)
- ADF OxyContin® (oxycodone extended-release) particles also form a gel when subjected to an aqueous environment

Image source: https://motherboard.vice.com/en_us/article/jppbxk/how-big-pharma-hooked-america-on-legal-heroin

Agonist/Antagonist Combination Example

- Embeda® (morphine ER/naltrexone) contains naltrexone as an opioid antagonist to deter abuse.
- Naltrexone is not released unless the product is manipulated.
- If naltrexone is released, an opioid-tolerant patient may experience withdrawal.

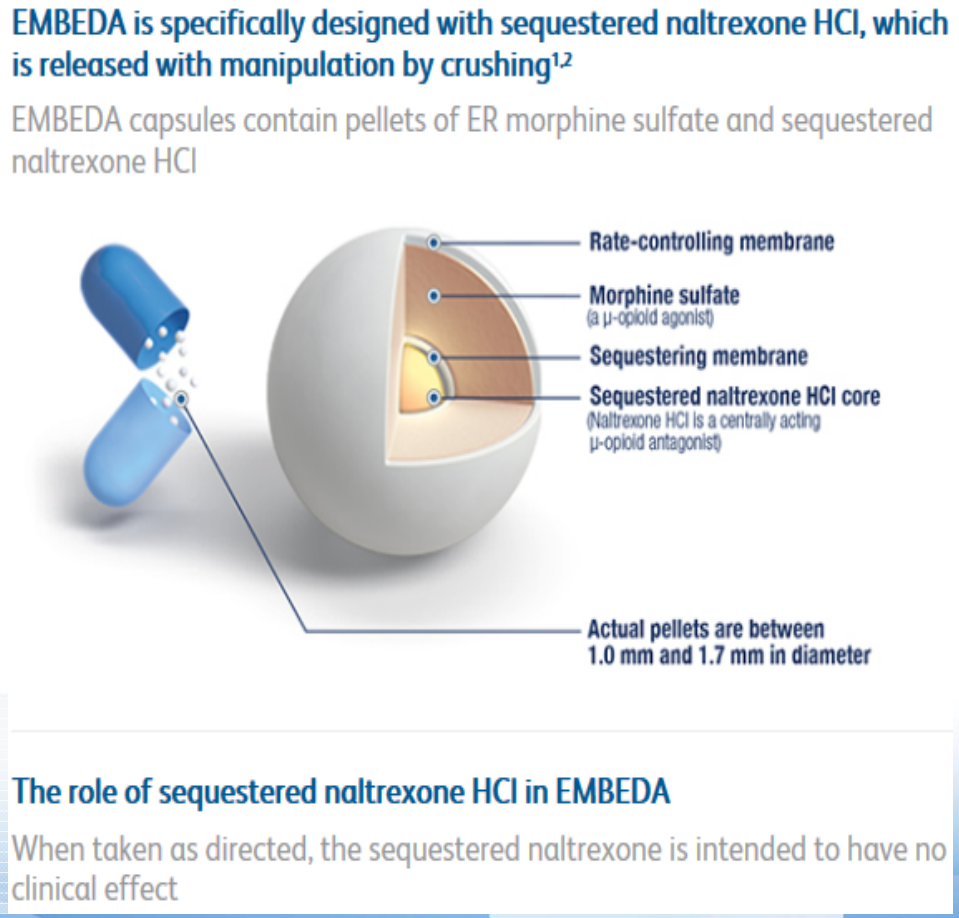


Image source: https://www.pfizerpro.com/product/embeda/hcp/technology

ADF Postmarket Studies (Category 4)

- Goal is to assess whether ADF actually results in meaningful reduction in abuse, misuse and the sequelae of abuse/misuse in the community
- Population-based, observational studies that should follow good epidemiological practices
- FDA may approve labeling describing the postmarket data showing reduced abuse or require removal of ADF labeling if abuse is not meaningfully deterred
- There is currently limited postmarket data for ADFs

Institute for Clinical and Economic Review (ICER) ADF Evidence Report

- Comparative net health benefit of ADF versus non-ADF (long-acting products only)
  - Individual Patient
    - OxyContin® (oxycodone extended-release) = C+ (comparable or better)
    - All other ADFs = P/I (promising but inconclusive)
  - Overall Population (including non-medical users)
    - All ADFs = I (inconclusive)
- Clinical abuse potential studies all showed reduced drug liking for ADFs versus non-ADFs
  - ICER noted there is no established threshold for what a clinically-important difference in any abuse potential endpoint
    - Clinical significance is unknown

ICER ADF Evidence Report Overview

- All Category 4 studies were for OxyContin® (oxycodone extended-release)
  - oEvidence is mixed for impact of OxyContin (oxycodone extended-release) on opioid abuse
    - Rates of OxyContin® (oxycodone extended-release) abuse decreased; however, abuse of other opioids and heroin may have increased
    - Diversion of OxyContin® (oxycodone extended-release) decreased after reformulation to ADF by as high as an 89% decrease by June 2015
    - Survey data from recreational users showed limited impact

ICER ADF Evidence Report – Diversion

- Severtson et al. 2013
  - –53% reduction in OxyContin® (oxycodone ER) diversion
  - –6% reduction in other opioid diversion
- Severtson et al. 2016
  - –89% reduction in OxyContin® (oxycodone ER) diversion
  - –27% reduction in other opioid diversion
- Coplan et al. 2016
  - –66% reduction in OxyContin® (oxycodone ER) diversion
  - –6% increase in other opioid diversion

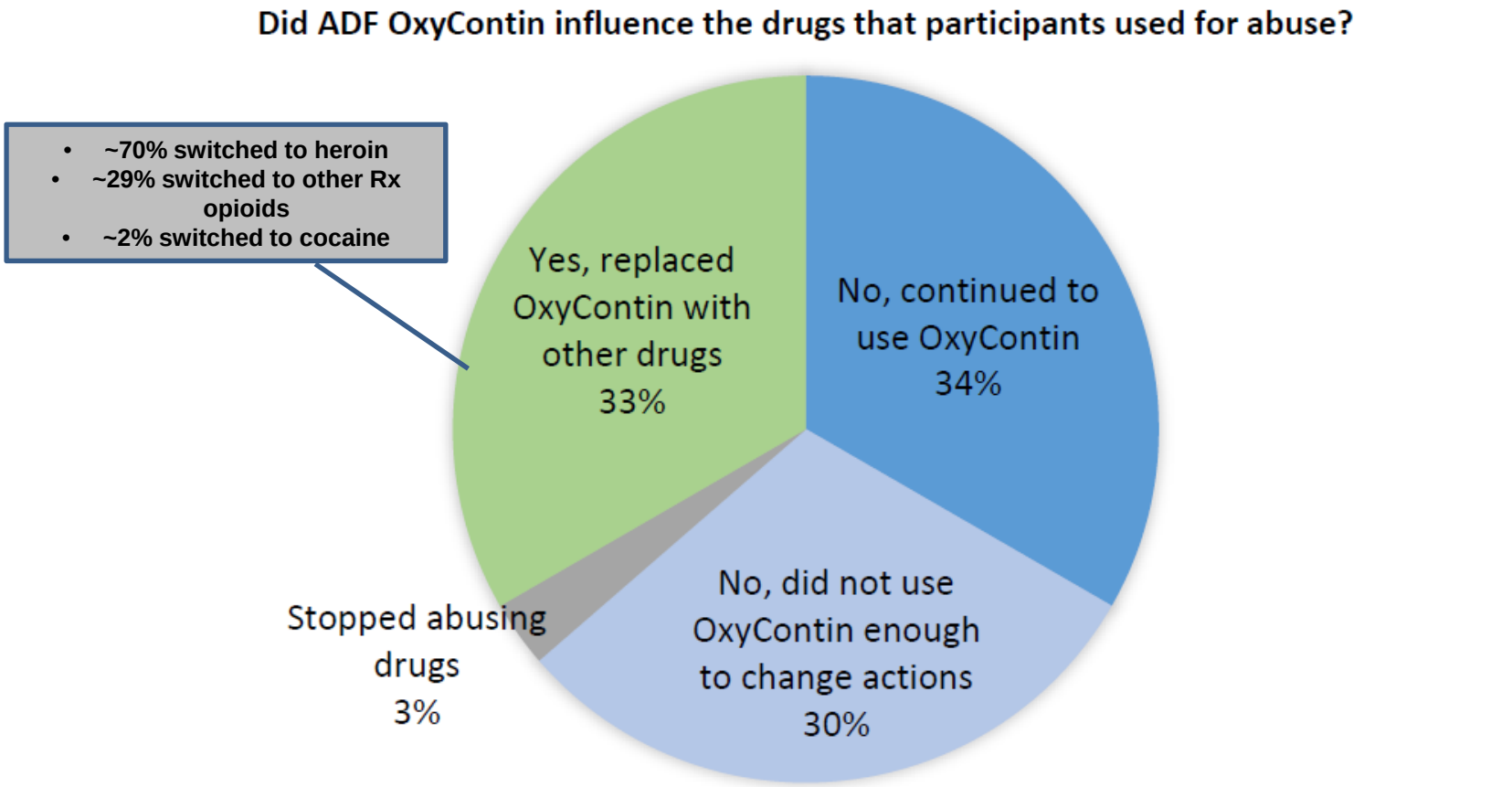
ICER ADF Evidence Report – Abuse

- All Category 4 studies showed a reduction in OxyContin® abuse post-reformulation to ADF
  - –Only 4 studies evaluated heroin abuse

Study	OxyContin® Abuse	Heroin Abuse	Other Rx Opioid Abuse (notable changes)
Cicero et al. 2015 and 2016	-42%	+100%	oxymorphone ER +38%
Cicero et al. 2012	-37%	+78%	all other Rx opioids +5%
Cassidy et al. 2014	-22%	-11%	oxymorphone ER +191%
Coplan et al. 2013	-36%	+42%	oxycodone (single entity) +20%

ICER ADF Evidence Report – Direct Survey Data

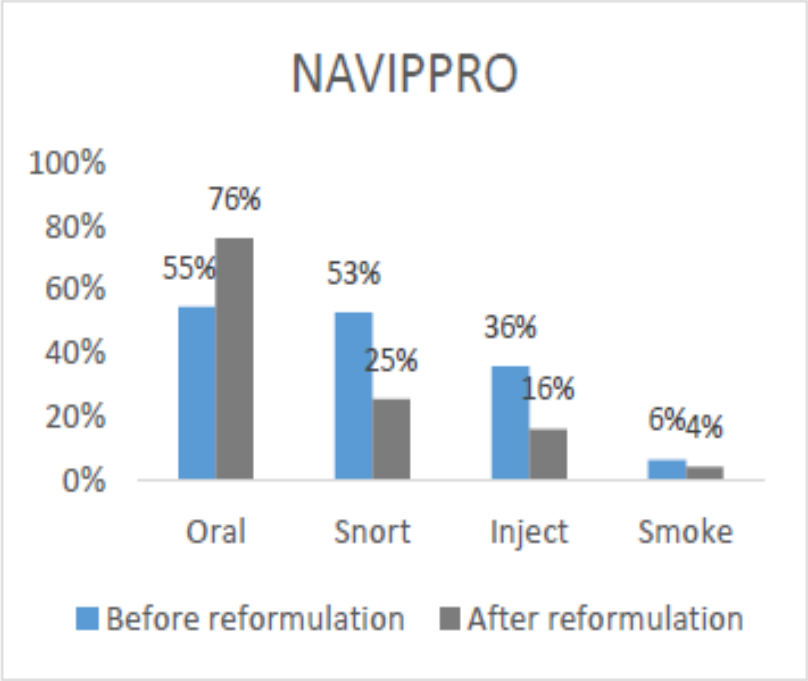
Figure 5. Follow Up Interview with RAPID Participants (N=153), Subset of RADARS SKIP [61]

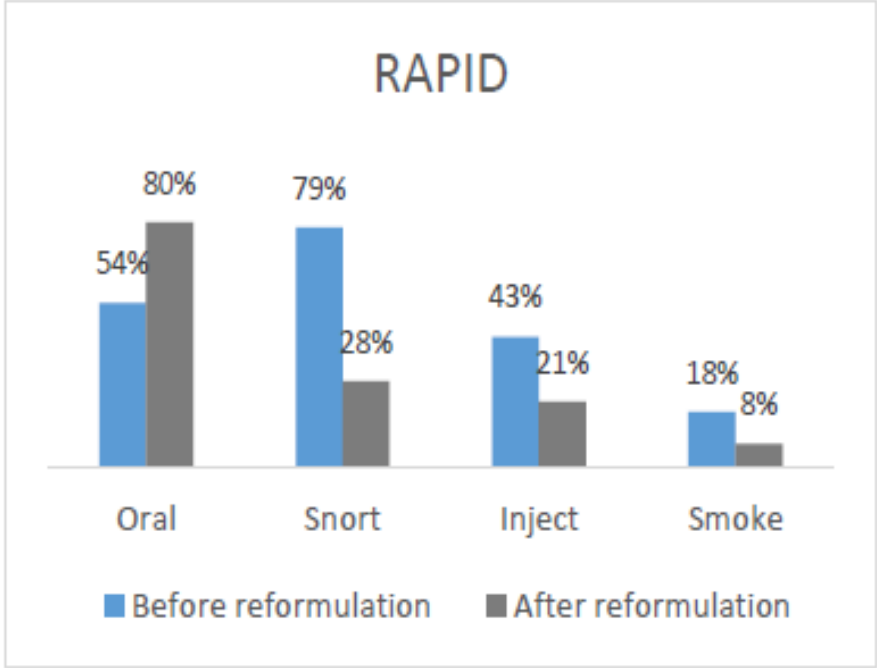


Source: https://icer-review.org/wp-content/uploads/2016/08/NECEPAC_ADF_Final_Report_08_08_17.pdf

ICER ADF Evidence Report – Route Switching

Figure 6. Changes in the Abuse Routes of OxyContin Among Participants Who Have Taken Pre- and Post-Reformulated Forms





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Quiz Question

What was ICER's net health benefit rating for ADFs for the entire population?

A. C+ (comparable or better)
B. P/I (promising, but inconclusive)
C. I (inconclusive)
D. None of the above

Quiz Question

What was ICER's net health benefit rating for ADFs for the entire population?

A. C+ (comparable or better)
B. P/I (promising, but inconclusive)
C. <u>I (inconclusive) – ICER noted ADFs causing net harm for the entire population could not be ruled out.</u>
D. None of the above

ICER ADF Economic Modeling

- Economic model for 100,000 chronic non-cancer pain patients newly prescribed either ADF or non-ADF opioids (long-acting only)
  - Cost to prevent one new abuse case = $231,514
  - Cost to prevent one overdose death = $1,362,339,569
- Cost neutrality could be achieved if ADF opioids were discounted by 41% from current market-basket price
- Massachusetts (MA) specific model
  - Converting all non-ADF to ADF
    - Total healthcare costs (including cost savings from decreased abuse-related costs with ADF) = Increase of $475,134,959
    - Cost to prevent one new abuse case = $599,131
- ICER did not include costs related to reduced diversion, which may be seen with ADFs

State ADF Legislative Activities

Passed Legislation	Legislation Vetoed	Legislation Introduced (active)
Florida	Maine (veto over-ridden)	Illinois
Maine	New Jersey	Indiana
Maryland	New York	Iowa
Massachusetts		Kansas
West Virginia		Kentucky
		Michigan
		New Jersey
		Oregon
		Pennsylvania
		Texas

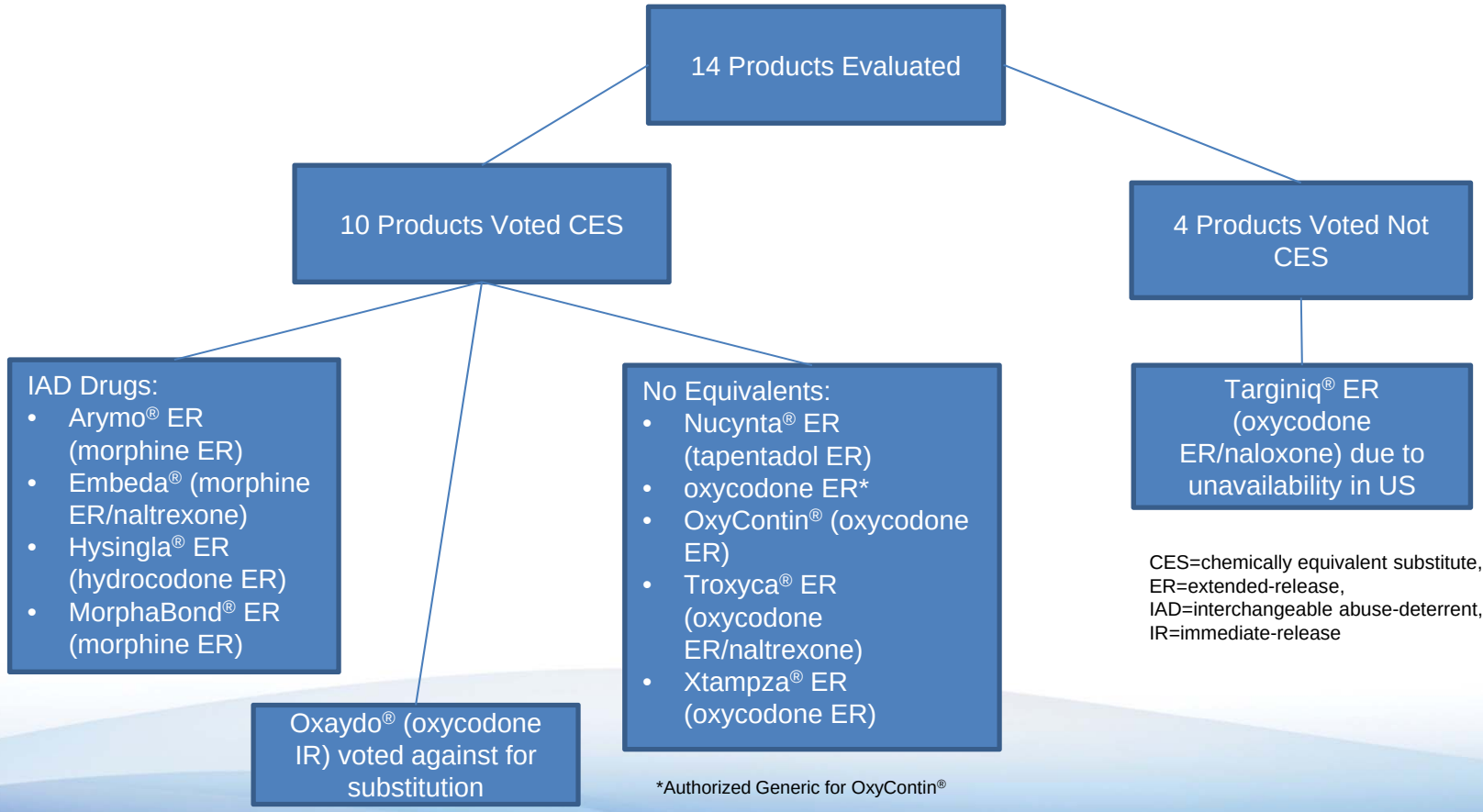
State ADF Laws

- Require payers to put ADFs at parity with non-ADFs:
  - Florida
    - Prior authorization (PA) only allowed on ADFs if non-ADFs also on PA
  - Maine
    - ADF coverage “not less favorable” than non-ADF coverage
    - No increase in cost sharing to accomplish this
  - Maryland
    - Two brand and generic (if available) ADFs must be covered per plan without a trial of another opioid required
  - Massachusetts
    - ADF coverage “not less favorable” than non-ADF coverage
    - Substitution of ADF for non-ADF
  - West Virginia
    - At least one ADF per active opioid ingredient must be covered
    - Lowest cost-sharing tier
    - No non-ADF trial required before ADF

Massachusetts Drug Formulary Commission (DFC)

- Chapter 258 of the Acts of 2014
  - oDFC to create formulary of chemically equivalent substitutes (CES) with abuse-deterrent properties for opioids with a heightened public health risk (HPHR opioids/non-ADFs).
  - oDFC has evaluated 14 drug products
    - 10 voted as potential CES
      - ➢4 CES voted as interchangeable abuse-deterrent drugs (IAD)
      - ➢5 CES had no equivalent non-ADF opioid to substitute for
      - ➢1 CES voted to not be substitutable (not IAD) based on weaker evidence and considered cost prohibitive
    - 4 voted against → not considered CES
  - oFormulary regulation currently in promulgation phase

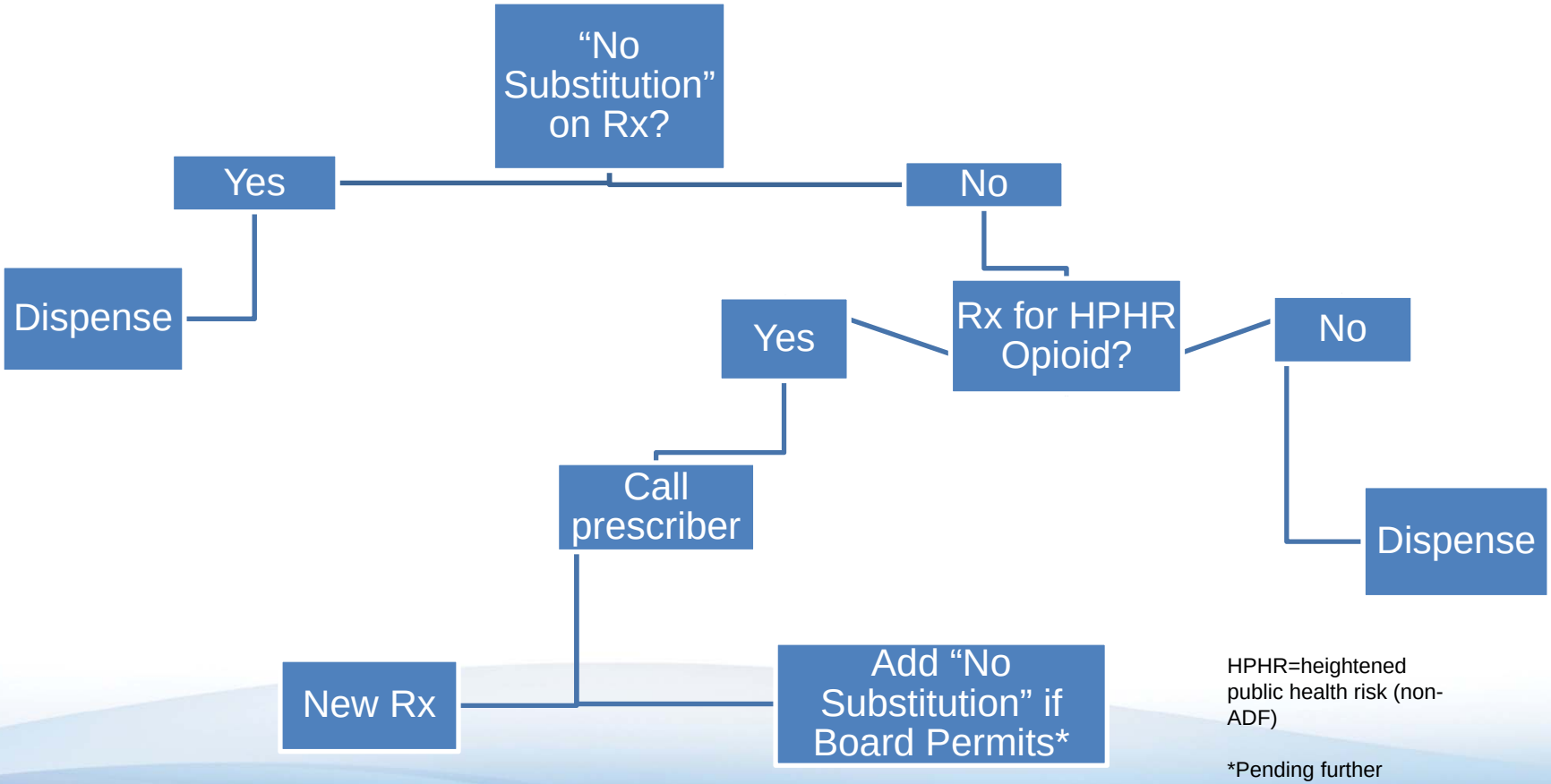
DFC Voting Summary



*Authorized Generic for OxyContin®

CES=chemically equivalent substitute,
ER=extended-release,
IAD=interchangeable abuse-deterrent,
IR=immediate-release

DFC Formulary Pharmacy Practice Implications



HPHR=heightened public health risk (non-ADF)

*Pending further guidance from Board of Registration in Pharmacy

Conclusion

- ADFs are effective options for the treatment of pain
  - May have the potential to reduce abuse, based upon surrogate endpoints
- Postmarket studies confirming ADFs reduce abuse in the community are limited, and available data is mixed.
  - Abuse and diversion of the ADF typically decrease
  - Abuse may shift from the ADF to other opioids/heroin
    - Changes in heroin abuse rates ranged from -11% to +100% after OxyContin® (oxycodone extended-release) reformulation
      - Study with 11% decrease in heroin abuse showed 191% increase in oxymorphone extended-release abuse.
- Widespread adoption of ADFs is likely to substantially increase healthcare costs, according to ICER
- Five states have passed legislation that will promote increased use of ADFs
  - At least 10 other states have active bills

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