Drug Safety and Risk Management Advisory Committee (DSaRM)

January 24-25, 2013

QUESTIONS

1. **(DISCUSSION)** Please discuss what the pharmacology data and the epidemiology data suggest about the potential for abuse of hydrocodone combination products compared with drugs that are currently in schedule II.

2. **(DISCUSSION)** Please discuss what impact rescheduling of hydrocodone combination products from schedule III to II would have on the following:
   a. Prescribing patterns for opioids, including hydrocodone combination products.
   b. Delivery of healthcare in the US, including impacts on drug distribution, manufacturing, prescription and dispensing by pharmacies.
   c. Availability of hydrocodone combination products for patients with appropriate needs for them as well as by individuals seeking to abuse opioids.
   d. Abuse and misuse of opioids, especially hydrocodone combination products.

3. **(DISCUSSION)** Please discuss whether there are other activities that could reduce abuse and misuse of these products?

4. **(VOTING)** Based on the background materials, presentations and the discussion above, do you recommend that hydrocodone combination products be rescheduled from schedule III to schedule II of the Controlled Substances Act (CSA)? Please explain the basis for your vote.

Controlled Substances Act Scheduling Process

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FDA Office of the Chief Counsel

Controlled Substances Act (CSA)

- First enacted in 1970 to regulate the manufacture, importation, possession, use, and distribution of certain substances
- While DEA is primarily responsible for interpreting and enforcing the CSA, HHS has a number of responsibilities, several of which are performed by FDA

Drug Scheduling Process

- FDA completes a medical and scientific evaluation and scheduling recommendation for HHS with the concurrence of the National Institute on Drug Abuse (NIDA)
- The HHS scheduling recommendation is binding on DEA as to scientific and medical matters and DEA cannot schedule a substance if HHS recommends that it not be controlled
- DEA schedules substances through rulemaking

CSA Schedules

- 5 Schedules under the CSA
- Schedule I is the most restrictive and substances in schedule I do not have a currently accepted medical use in treatment in the United States
- Drugs with abuse potential that have a currently accepted medical use in treatment in the United States (e.g., FDA approval) are controlled in schedules II through V

CSA Schedules (Cont.)

- A substance's schedule dictates the requirements regarding physical security, quotas, prescription, and registration requirements
- Section 202 of the CSA and DEA regulations at 21 CFR Part 1308 list the substances that are controlled in each schedule

CSA Eight Factors

1. Its actual or relative potential for abuse
2. Scientific evidence of its pharmacological effect, if known
3. The state of current scientific knowledge regarding the drug or substance
4. Its history and current pattern of abuse
5. The scope, duration, and significance of abuse
6. What, if any, risk there is to the public health
7. Its psychic or physiological dependence liability
8. Whether the substance is an immediate precursor of a substance already controlled

CSA Eight Factors (Cont.)

Secretary shall consider these factors:

2. Scientific evidence of its pharmacological effect, if known
3. The state of current scientific knowledge regarding the drug or substance
6. What, if any, risk there is to the public health
7. Its psychic or physiological dependence liability
8. Whether the substance is an immediate precursor of a substance already controlled

CSA Eight Factors (Cont.)

Secretary of HHS shall consider the scientific or medical considerations involved in:

1. Its actual or relative potential for abuse
4. Its history and current pattern of abuse
5. The scope, duration, and significance of abuse

CSA Eight Factors (Cont.)

1. Its actual or relative potential for abuse -
   - Individuals are taking the substance in amounts sufficient to create a hazard to their health, the safety of others, or the community
   - Significant diversion from legitimate drug channels
   - Individuals are taking the substance on their own initiative rather than on the basis of medical advice from a licensed practitioner
   - Related in its action to a substance already listed as having a potential for abuse
     - likely that it will have the same potential for abuse
     - reasonable to assume that there may be significant diversions, use contrary to or without medical advice, or substantial capability of creating hazards to user's health or community's safety

Scheduling Recommendation

- After considering the eight factors, HHS must make a recommendation as to the appropriate schedule
- Each schedule has three findings that must be made
- The findings for each schedule are set out in section 202 of the CSA

Schedule Findings

- **Schedule I**

  High potential for abuse

  No currently accepted medical use in treatment in the U.S.

  Lack of accepted safety for use under medical supervision

Schedule Findings (Cont.)

- **Schedule II**

  High potential for abuse

  Currently accepted medical use in treatment in the U.S. or a currently accepted medical use with severe restrictions

  Abuse of the substance may lead to severe psychological or physical dependence

- **Schedule III**

  Potential for abuse less than drugs or substances in schedules I or II

  Currently accepted medical use in treatment in the U.S.

  Abuse of the substance may lead to moderate or low physical dependence or high psychological dependence

Schedule Findings (Cont.)

- **Schedule IV**

  Low potential for abuse relative to substances in schedule III

  Currently accepted medical use in treatment in the U.S.

  Abuse of the substance may lead to limited physical dependence or psychological dependence relative to substances in schedule III

- **Schedule V**

  Low potential for abuse relative to substances in schedule IV

  Currently accepted medical use in treatment in the U.S.

  Abuse of the substance may lead to limited physical dependence or psychological dependence relative to the substances in schedule IV

Hydrocodone Scheduling

- Controlled Substances Act
  - Places hydrocodone in Schedule II
  - Places hydrocodone combination products containing up to 15 mg or 3 mg/ml of hydrocodone in Schedule III

Requirements	Schedule I	Schedule II	Schedule III	Schedule IV	Schedule V
Registration	Required	Required	Required	Required	Required
Recordkeeping	Separate	Separate	Readily Retrievable	Readily Retrievable	Readily Retrievable
Distribution Restrictions	Order Forms	Order Forms	Records Required	Records Required	Records Required
Dispensing Limits	Research use only	Rx: written No Refills 90-day supply	Rx: written or oral Refills with MD's authorization	Rx: written or oral Refills with MD's authorization	OTC (Rx drugs limited to MD's order)
Manufacturing Security	Vault/Safe	Vault/Safe	Secure Storage	Secure Storage	Secure Storage
Manufacturing Quotas	Yes	Yes	No (Some drugs limited by Schedule II)	No (Some drugs limited by Schedule II)	No (Some drugs limited by Schedule II)
Import/Export Narcotic	Permit	Permit	Permit	Permit	Permit to import, declaration to export
Reports to DEA (Narcotic) Mfr.& Distributor	Yes	Yes	Yes	Mfr. only	Mfr. Only

C-II and C-III Regulation Differences

- Manufacturer Security
  - Largest compliance issue for C-III to C-II
  - Security specifications for a CII vault are very strict and require significant investment
- Recordkeeping for distribution and sales
- C-II: Written prescription (with limited exceptions for emergencies) and no refills (3 Rxs for a maximum 90-day supply)
- C-III: Written or oral prescription and 5 refills in 6 months

Timeline

- 2004 –DEA requested that HHS prepare scientific and medical evaluation and scheduling recommendation
- 2008 – HHS recommendation to maintain hydrocodone combination products in Schedule III
- 2009 – DEA submitted new data to HHS and requested re-evaluation
- 2012 – FDA announced a public advisory committee meeting to consider the public health benefits and risks, including the potential for abuse, of drugs containing hydrocodone either combined with other analgesics or as an antitussive

Food and Drug Administration Safety and Innovation Act (FDASIA) (Public Law 112-144)

- Signed into law July 9, 2012
- Section 1139 “Scheduling of Hydrocodone”
  - Requires FDA to hold a public meeting
  - Solicit advice and recommendations to assist in conducting a scientific and medical evaluation and scheduling recommendation to DEA regarding drug products containing hydrocodone, combined with other analgesics or as an antitussive

FDASIA Section 1139 (Cont.)

- FDA to solicit input from a variety of stakeholders including patients, health care providers, harm prevention experts, NIDA, CDC, & DEA regarding the health benefits and risks, including the potential for abuse and the impact of rescheduling these hydrocodone products from Schedule III to Schedule II
- FDA to post the transcript of this meeting on its website

Key Reminders

- In the scientific and medical evaluation and scheduling recommendation, HHS must make three findings:
  - **Schedule II**
    - High potential for abuse
    - Currently accepted medical use in treatment in the U.S. or a currently accepted medical use with severe restrictions
    - Abuse of the substance may lead to severe psychological or physical dependence
  - **Schedule III**
    - Potential for abuse less than drugs or substances in schedules I or II
    - Currently accepted medical use in treatment in the U.S.
    - Abuse of the substance may lead to moderate or low physical dependence or high psychological dependence

Overview of DEA's Request for Rescheduling Hydrocodone Combination Products from Schedule III to Schedule II of the Controlled Substances Act (CSA)

Silvia N. Calderon, Ph.D.
Team Leader. Controlled Substance Staff
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Outline

- Schedule status of hydrocodone combination and currently available products
- Drug Enforcement Administration (DEA) and Food and Drug Administration (FDA) roles on the rescheduling petition
- 2008 Department of Health and Human Services (HHS) recommendation
- 2009 DEA analysis and request for re-evaluation of the data provided in the 2008 HHS recommendation
- Controlled Substance Staff (CSS) overview on the abuse potential of hydrocodone
- Office of Surveillance and Epidemiology (OSE) overview on availability of hydrocodone products and epidemiological analysis
- Summary and points to consider

Schedule Status of Hydrocodone Substance and Combination Products

- Congress placed hydrocodone in two different Schedules in the CSA
  - Schedule II
    - Hydrocodone *substance*
  - Schedule III
    - Hydrocodone (in specified amounts) in combination with an isoquinoline alkaloid of opium (specified amounts), or
    - Hydrocodone (in specified amounts) in combination with one or more therapeutically active non-narcotic ingredients

Schedule III Hydrocodone Combination Products

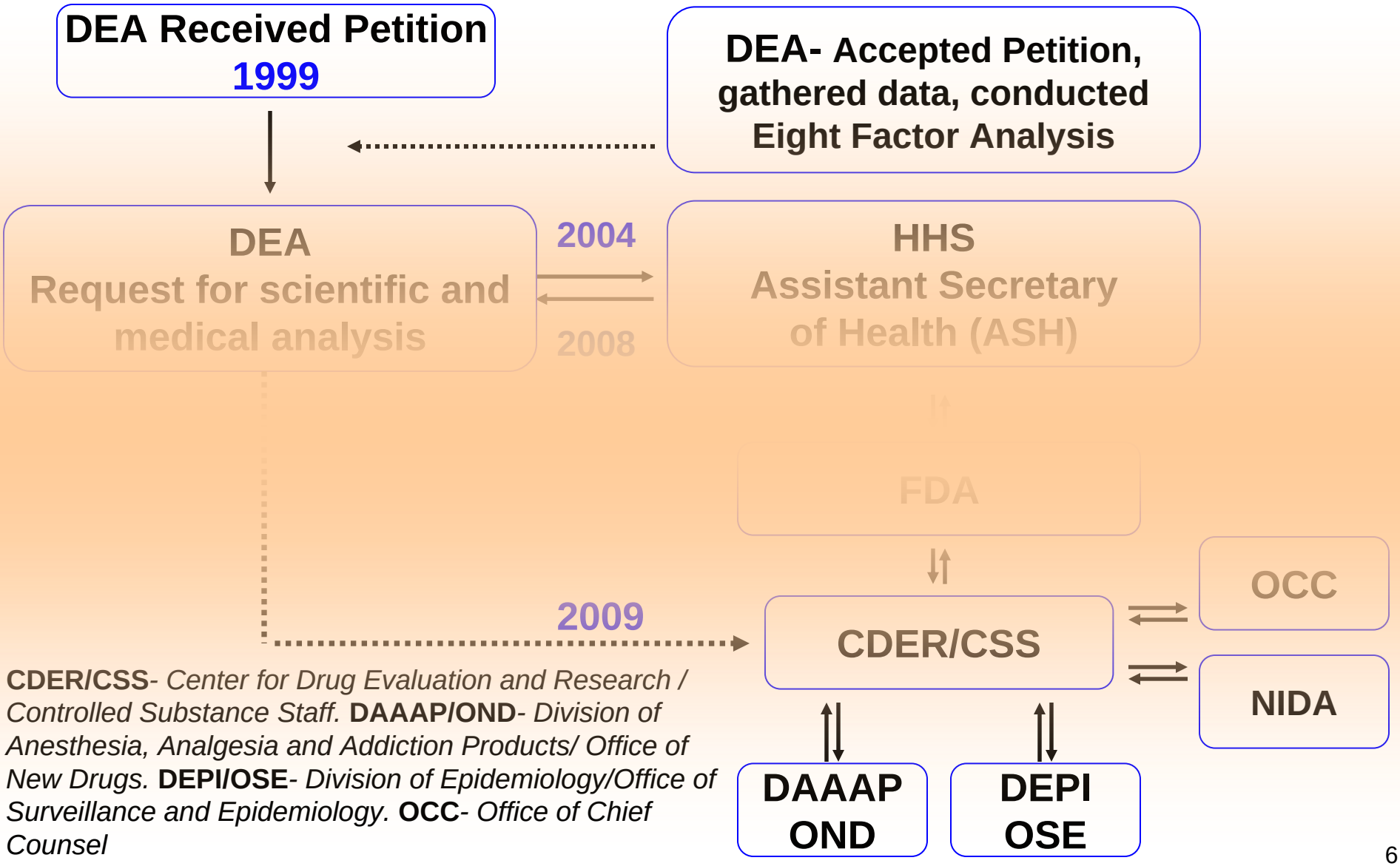
- Schedule III – 21 CFR 1308.13 (e) Narcotic Drugs. Unless specifically excepted or unless listed in another schedule:

  (1) Any material, compound, mixture, or preparation containing any of the following narcotic drugs, or their salts calculated as the free anhydrous base or alkaloid, in limited quantities as set forth below

  (iv) Not more than 300 milligrams of dihydrocodeinone (hydrocodone) per 100 milliliters or not more than 15 milligrams per dosage unit, with one or more active nonnarcotic ingredients in recognized therapeutic amounts

Currently Available Hydrocodone Combination Products

- Analgesic products
  - 81 products approved containing up to 10 mg of hydrocodone bitartrate per dosage unit and acetaminophen or ibuprofen.
  - All but one are generic products
  - All immediate release formulations
- Cough suppressants products
  - 12 products approved containing up 10 mg of hydrocodone bitartrate per dosage unit and chlorpheniramine, homatropine or pseudoephedrine.
  - All but three are generic products
  - Immediate and extended release formulations



CDER/CSS- *Center for Drug Evaluation and Research / Controlled Substance Staff.* **DAAAP/OND**- *Division of Anesthesia, Analgesia and Addiction Products/ Office of New Drugs.* **DEPI/OSE**- *Division of Epidemiology/Office of Surveillance and Epidemiology.* **OCC**- *Office of Chief Counsel*

2008 HHS Recommendation

- Recommended to maintain hydrocodone combination products in Schedule III of the CSA
- Recommendation based upon three findings:
  1) Hydrocodone combination products have a lower potential for abuse than drugs or other substances in Schedule II
  2) Currently accepted medical use in treatment in the U.S.
  3) Abuse of hydrocodone combination products may lead to moderate or low physical dependence or high psychological dependence

2009 DEA Analysis and Request for Re-evaluation

- In 2009, DEA submitted an analysis with updated data, and requested that CDER re-evaluate the 2008 HHS recommendation
- DEA analysis and request for re-evaluation focus primarily on the following areas:
  - Abuse potential of hydrocodone
  - Availability of hydrocodone combination products
  - Epidemiological analysis of actual indicators of abuse in the 2008 HHS recommendation

2009 DEA Analysis and Request for Re-evaluation

- Regarding the abuse potential of hydrocodone combination products:
  - DEA states that hydrocodone substance and in combination produce similar abuse related effects to other Schedule II opioids (morphine, oxycodone and hydromorphone)
    - Based on the review of human abuse potential studies cited in the 2008 HHS recommendation

CSS Overview
Abuse Potential of Hydrocodone

- CSS reviewed six studies published from 2003 to date and concluded that hydrocodone single entity and in combination produce:
  - Similar effects to those of typical Schedule II opioid agonists in a ***dose-related*** manner
  - Subjective abuse-related effects such as “high” and “liking” are observed at doses of hydrocodone bitartrate equal to or greater than 15 mg when taken orally
    - Current products on the market contain less than 15 mg of hydrocodone bitartrate per dosage form (10 mg highest strength available)

2009 DEA Analysis and Request for Re-evaluation

- Regarding the availability of hydrocodone combination products
  - DEA states that "*the diversion, trafficking and abuse of hydrocodone and oxycodone are mainly associated with pharmaceutical products manufactured, distributed and prescribed within the U.S. There is no clandestine production of these substances. The production and prescription of these products have increased dramatically in recent years*"

OSE Overview
Availability of Hydrocodone Products

- Hydrocodone/ acetaminophen products are widely prescribed. In 2011,
  - Approximately 131 million prescriptions for hydrocodone combination analgesics *vs.* 34.6 million for oxycodone combination products
  - 47 million patients received hydrocodone combination products *vs.* 15.1 million patients receiving oxycodone combination products

(*Source*: IMS, Vector One®: National (VONA) and IMS Health, Total Patient Tracker)

2009 DEA Analysis and Request for Re-evaluation

- In the 2009 request for re-evaluation, DEA included an epidemiological analysis. In this analysis, DEA
  - Measured levels of abuse using "*abuse ratios*"
    - "*Abuse ratios*" measure the occurrence of an abuse related event (*numerator*) per amount of drug available for abuse (*denominator*)
    - Relative to other drugs with similar pharmacology and medical use (*comparator products*)
  - Calculated "*abuse ratios*" using different *denominators* from those in the 2008 HHS Recommendation, and oxycodone products as the only *comparators*
  - Concluded that *"the non-narcotic active ingredients present in hydrocodone combination products do not reduce the abuse potential of hydrocodone"*

OSE Overview
Epidemiological Analysis

- OSE also calculated "*abuse ratios*"
  - One *comparator* - Oxycodone containing products (Schedule II)
  - Drug abuse-related outcomes (*numerator*) for specific drug products
  - Amount of drug available for abuse (*denominator*)
    - The selection of *denominators* to evaluate levels of abuse of hydrocodone combination products relative to other opioid products constitutes the major point in the 2009 DEA analysis and request for re-evaluation

OSE Overview
Epidemiological Analysis

- OSE identified:
  - The number of abuse-related *Emergency Department (ED) visits* in the *Drug Abuse Warning Network (DAWN)* as the *numerator* that best captures abuse-related events for specific prescription drug products (hydrocodone combination *vs*. oxycodone single entity, immediate release and extended release, *vs.* oxycodone combination)
  - The *Total Number of Dispensed Units* (e.g. tablets, capsules) as the *denominator* that likely provides the best metric of units available for abuse

OSE Overview
Epidemiological Analysis

- OSE analysis shows that:
  - Hydrocodone products are widely abused
  - "*Abuse ratios*" for hydrocodone combination analgesic products are lower than those for oxycodone containing products
  - Comparison of "*abuse ratios*" for oxycodone and tramadol single entity products to those of oxycodone and tramadol combination products shows that the addition of a non-narcotic ingredient (acetaminophen) reduces the levels of abuse of these opioids

Summary and Points to Consider

- No single test or analysis can provide a full characterization of the abuse potential of a drug
- Assessment of the relative abuse potential of hydrocodone combination products needs to consider the pharmacology and abuse-related effects, medical use and availability, levels of abuse, and consequences of abuse
- Hydrocodone combination products fulfill an important role in the management of pain, as evidenced by the number of prescriptions dispensed yearly and the number of patients being prescribed these products

Summary and Points to Consider

- The consequences of re-scheduling hydrocodone combination products on patient access and proper management of pain need to be considered
- Alternatives to re-scheduling these products, such as educational efforts and use of Prescription Monitoring Programs, may prove effective in reducing the levels of abuse of hydrocodone containing products

Drug Utilization Patterns for Combination Hydrocodone-Containing Products and Selected Opioid Analgesics, Years 2007-2011

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Drug Safety and Risk Management Advisory Committee (DSaRM)
January 24-25, 2012

Outline

- Sales Distribution
- Prescription and Patient trends
- Prescriber Specialty
- Duration of Therapy
- Diagnosis
- Limitations
- Summary

Sales Data

Years 2007-2011

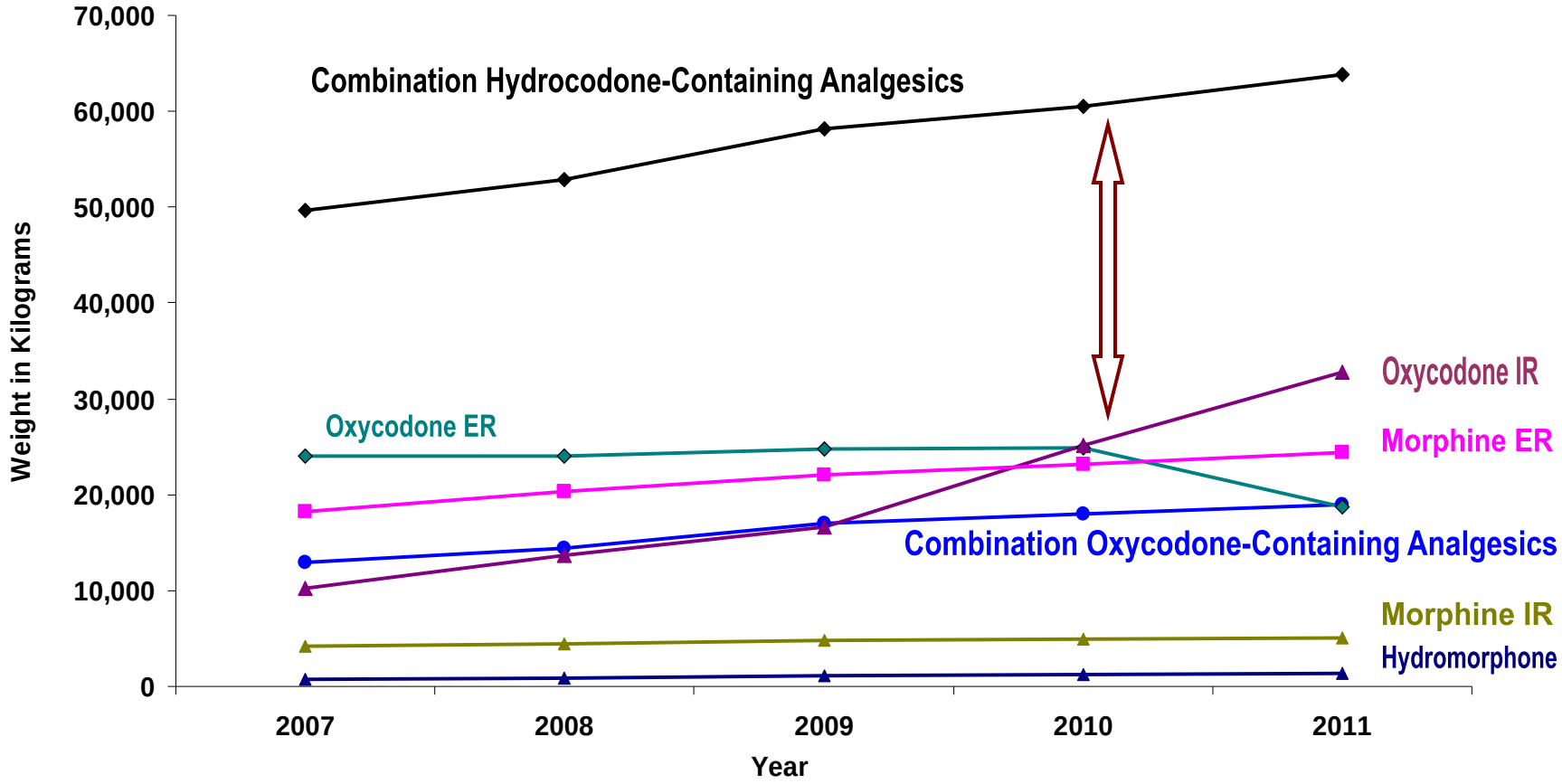
IMS Health, IMS National Sales Perspective™

IMS Health, IMS National Sales Perspectives™

Measures sales data from *manufacturer to retail and non-retail channels of distribution*

- Retail Channels - chain, independent, mass merchandisers, food stores with pharmacies
- Non-Retail Channels - federal facilities, non-federal hospitals, clinics, long-term care facilities, home health care, HMOs, miscellaneous channels (prisons, universities, other)

Weight in Kilograms (KG) of Selected Opioid Analgesics Sold from Manufacturers to Channels of Distribution, Years 2007-2011

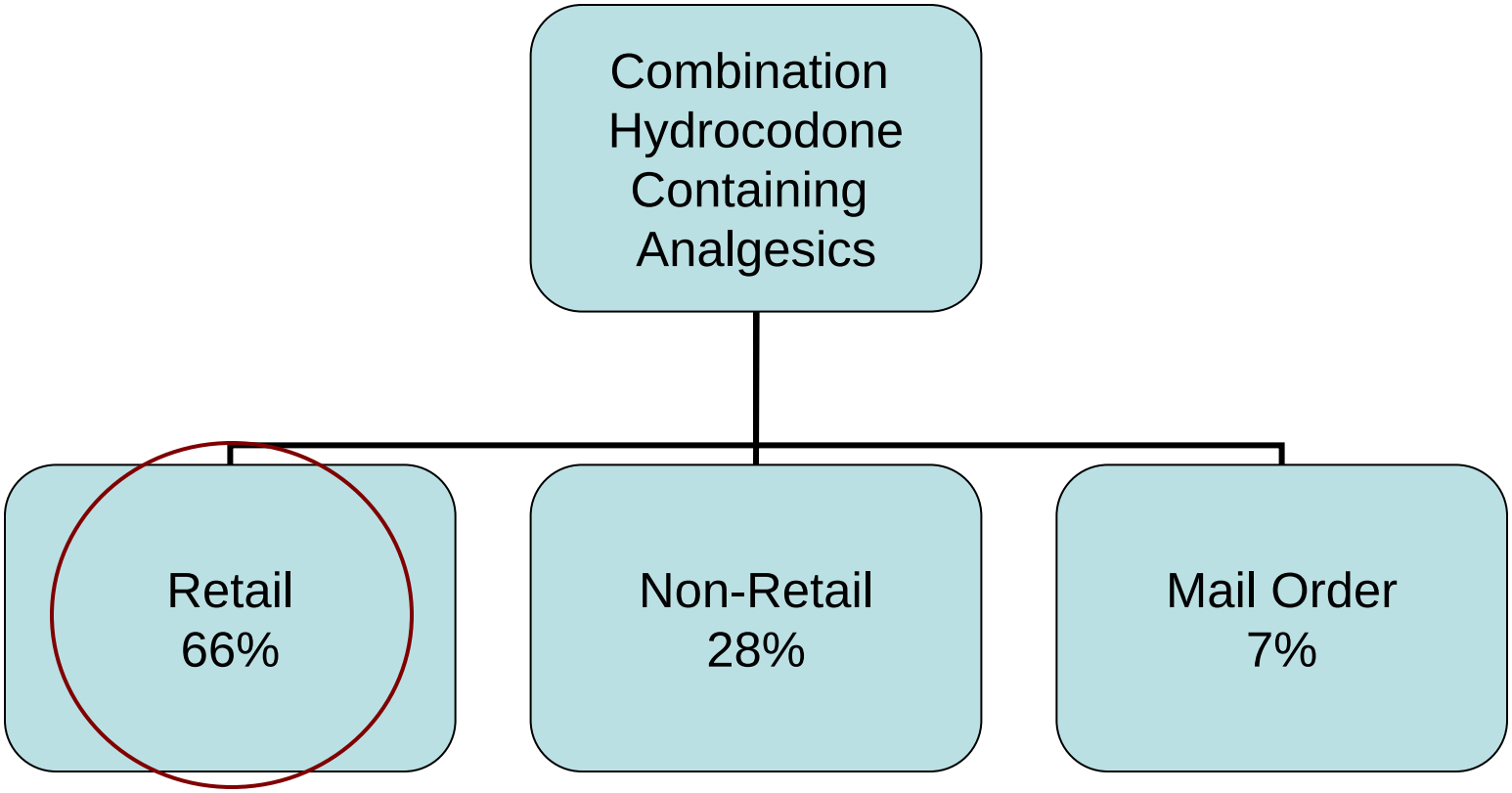


IMS Health, IMS National Sales Perspectives™. Data Extracted April 2012

Sales Data

Year 2011

*IMS Health, National Sales Perspective™, Extracted October 2012**



** Total may add to more than 100% due to rounding*

Prescription and Patient Level Data

Outpatient Retail Pharmacies
Years 2007-2011

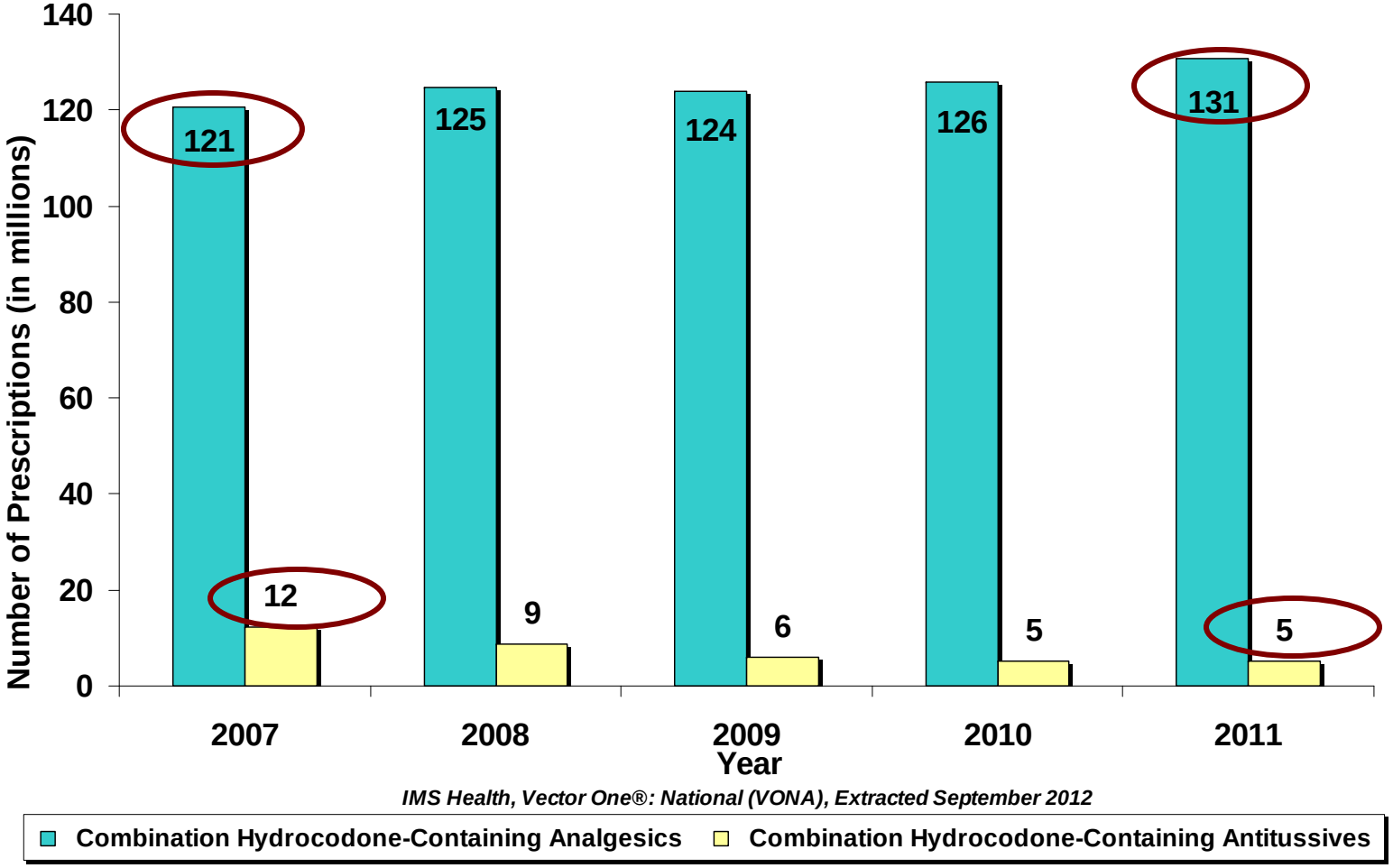
IMS Health, Vector One®: National (VONA)
and Total Patient Tracker (TPT)

IMS Health, Vector One®: National (VONA) and Total Patient Tracker (TPT)

Measures dispensing of prescriptions *out of retail pharmacies into the hands of consumers*

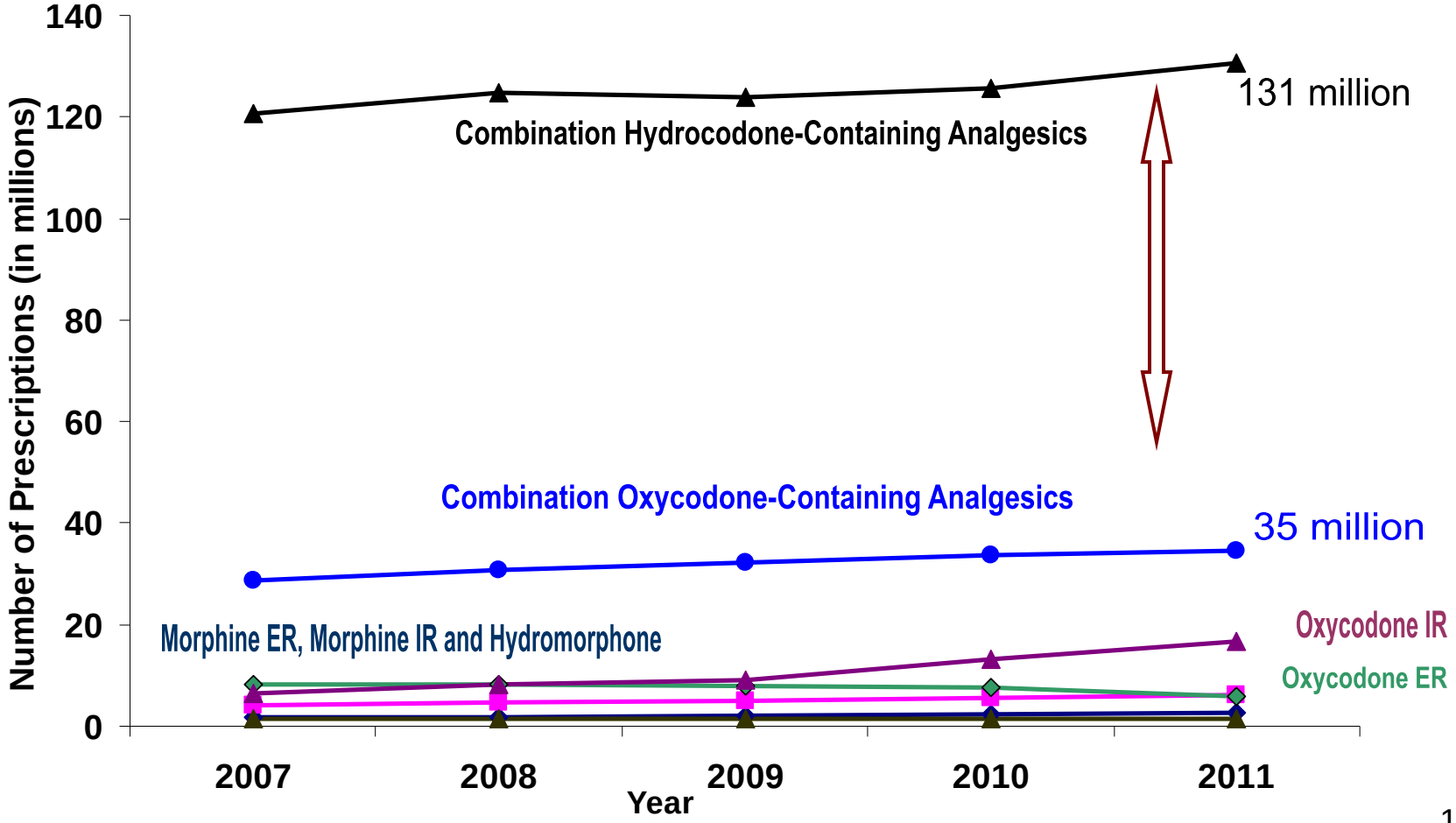
- National-level projected prescription and patient-centric tracking service
- 59,000 U.S. retail pharmacies

Number of Prescriptions for Combination Hydrocodone-Containing Products (Analgesics and Antitussives) Dispensed from U.S. Outpatient Retail Pharmacies, Years 2007-2011



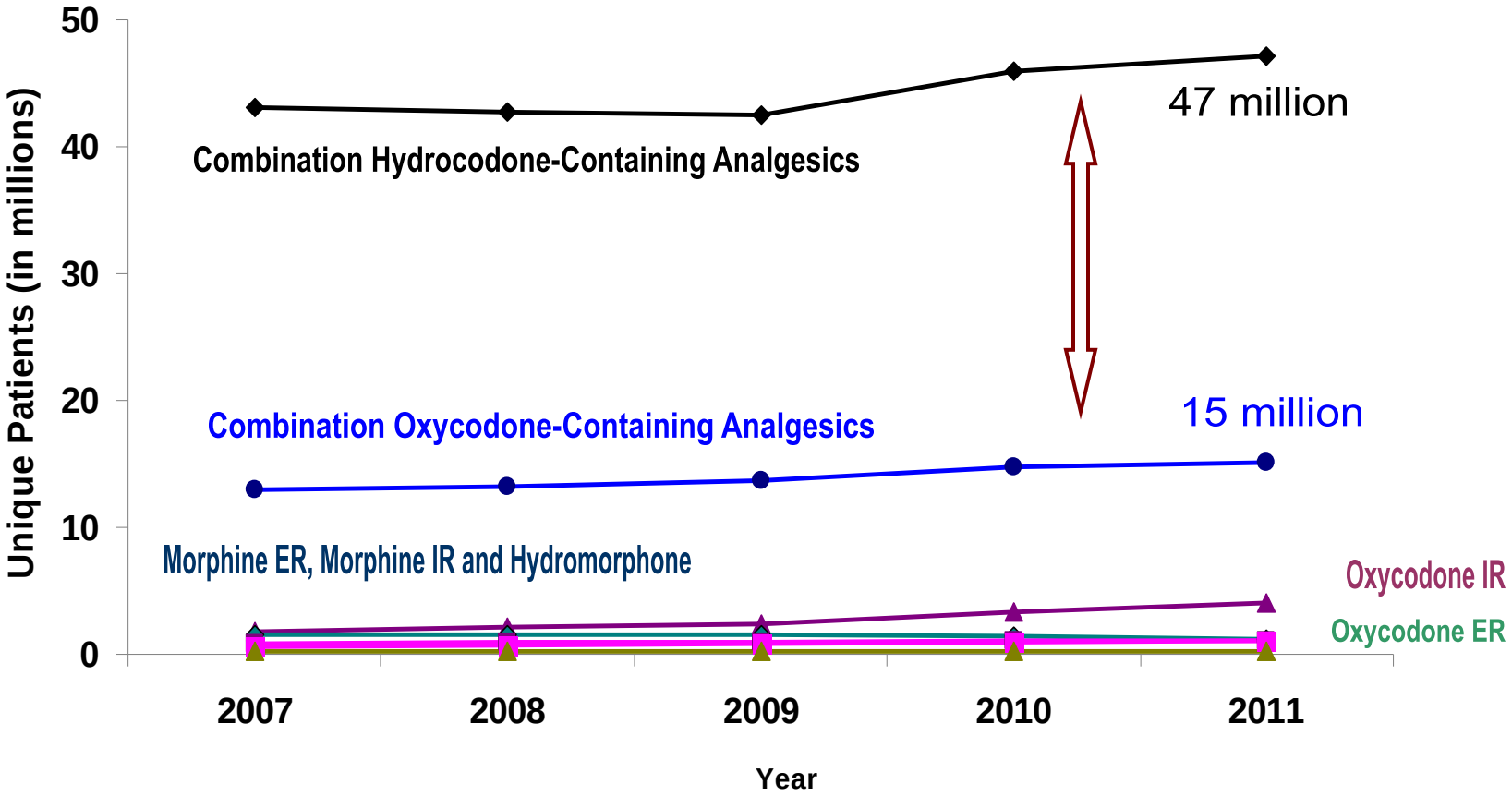
IMS Health, Vector One®: National (VONA), Extracted September 2012

Number of Prescriptions for Combination Hydrocodone-Containing Analgesics and Selected Opioid Analgesics Dispensed Through U.S. Outpatient Retail Pharmacies, Years 2007-2011



IMS Health, Vector One®: National (VONA). Extracted September 2012

Number of Patients Receiving a Dispensed Prescription for Combination Hydrocodone-Containing Analgesics and Selected Opioid Analgesics through U.S. Outpatient Retail Pharmacies, Years 2007-2011



IMS Health, Total Patient Tracker. Extracted September 2012

Prescriber Specialty Data

Outpatient Retail Pharmacies
Years 2007-2011

IMS Health, Vector One®: National (VONA)

Percentage of Prescriptions Dispensed for Combination Hydrocodone-Containing Analgesics and Selected Opioid Analgesics by Prescriber Specialty Through U.S. Outpatient Retail Pharmacies, Years 2007-2011, Cumulative

	Hydrocodone Combination	Oxycodone Combination	Oxycodone IR	Oxycodone ER	Morphine IR	Morphine ER	Hydromorphone
	Share %	Share %	Share %	Share %	Share %	Share %	Share %
General Practice/Family Practice/Osteopathy	25.6	18.7	23.3	26.8	25.1	24.7	17.3
Internal Medicine	14	12.5	14.8	16.9	17.8	14.9	14.7
Dentist	10	5.3	0.3	0.1	0.1	0.1	0.5
Orthopedic Surgery	8.3	8.9	4.4	4.1	0.7	1.2	5.2
Unspecified	5.6	5.9	8.1	6.2	7.3	7.2	6.8
Physician Assistant	3.8	5.0	4.9	3.8	3.2	4.6	5.0
Nurse Practitioner	3.3	3.6	5.6	5.0	5.4	6.7	4.4
Anesthesiologists	2.6	4.3	9.1	10.3	12.1	15.3	5.2
All Others	26.4	35.8	29.3	27.0	28.3	25.3	41.2

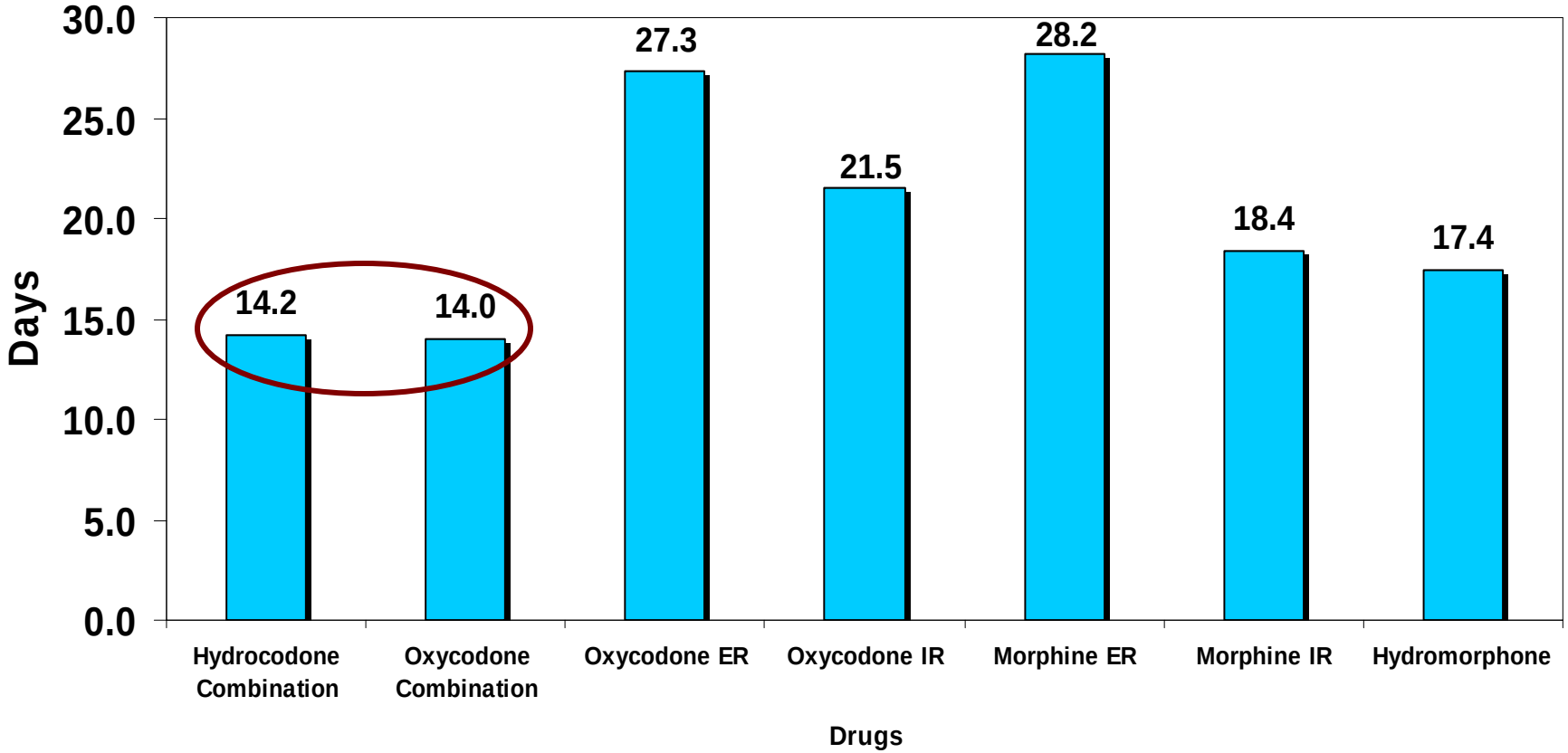
Source: IMS, Vector One®: National (VONA) Extracted September 2012.

Average Days of Therapy Dispensed Per Prescription

Outpatient Retail Pharmacies
Year 2011

IMS Health, Vector One®: National (VONA)

Average Number of Days of Therapy Dispensed Per Prescription for Selected Opioid Analgesics Through U.S. Outpatient Retail Pharmacies, Year 2011



IMS Health, Vector One®: National (VONA). Extracted September 2012

Distribution of Days of Therapy

Year 2010-2011

Source Healthcare Analytics Prometis Lx®

Source Healthcare Analytics Prometis Lx®

- **Measures *longitudinal* product use based on medical and prescription claims**
  - Commercial plans
  - Medicare Part D plans
  - Medicaid claims
  - Cash

Crude Days of Therapy for Combination Hydrocodone-Containing Analgesics and Selected Opioid Analgesics in a Sample of Patients,Years 2010-2011, cumulative

Source Healthcare Analytics ProMetis Lx®, Extracted January, 2012

Regimen	Number of Sample Patients	Days of Therapy Median	Average	Min	Max
Combination Hydrocodone-Containing Analgesics	16,281,353	8	45.1	2	730
Combination Oxycodone-Containing Analgesics	5,497,455	6	30.0	2	730
Oxycodone IR	1,168,258	19	72.4	2	730
Oxycodone ER	70,654	31	42.6	2	664

Diagnosis Data

January 2007 – November 2011

Encuity Research TreatmentAnswers™

Diagnosis Data

Encuity Research, Treatment Answers™

- Monthly survey that monitors disease states and physician intended prescribing habits on a national-level
- 3,200 panelists, 30 specialties, 115 pain specialists
- Includes diagnoses, patients characteristics, and treatment patterns

Diagnoses Associated with Combination Hydrocodone-Containing Analgesics and Selected Opioid Analgesics, January 2007-November 2011, Cumulative

	Hydrocodone Combination	Oxycodone Combination	Oxycodone IR	Morphine ER	Morphine IR
	N= 2,850,000	N= 1,406,000	N= 566,000	N= 2,618,000	N= 407,000
Diseases of the Musculoskeletal System and Connective Tissue (710-739)	25%	20%	41%	68%	56%
Disease of Respiratory System (462-493)	21%	2%			
Fractures, Sprains, Contusions, Injuries (800-999)	19%	26%	8%	3%	4%
Follow up examinations	10%	14%	2%	4%	5%
Headaches and Nerve Pain (337-359)	3%	4%	38%	15%	20%
Fever and General Symptoms (780-789)	3%	4%	5%	2%	6%
Neoplasms (140-239)	2%	0%	5%	4%	0%
Disease of Genitourinary System (592-626)	2%	22%		0%	2%
Bacterial, Viral and Parasitic Infections (001-138)	1%	0%	0%	0%	0%
All others	13%	7%	2%	2%	7%

Source: Encuity Research TreatmentAnswers™ , Extracted January 2012

Limitations

- Only outpatient opioid use assessed; inpatient, Emergency Department and other non-outpatient settings not included in analysis
- No statistical tests were performed to determine statistically significant changes over time

Summary

- In year 2011 approximately 131 million prescriptions and 47 million patients received combination hydrocodone-containing analgesics
  - Number of prescriptions and unique patients far exceeds other selected opioids
- Primary care practitioners prescribed about 40% of total combination hydrocodone-containing analgesic prescriptions
- Combination hydrocodone and oxycodone-containing analgesics appear to be used more often to treat acute pain conditions
- Single-ingredient opioid analgesics appear to be used more often for treatment of chronic pain conditions

OSE Epidemiologic Analysis of the Misuse/Abuse of Hydrocodone-containing Analgesics

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Epidemiologist
Division of Epidemiology II (DEPI-II)
Office of Surveillance and Epidemiology (OSE)

Review of Methods and Materials

- DEA's request: "Hydrocodone combination products: an eight-factor analysis"

- OSE review:
  - Focused on epidemiological methods used by DEA to assess abuse liability
  - Conducted additional analyses
  - Focused solely on combination hydrocodone-containing analgesics

DEA and OSE: Main Findings

- **DEA Conclusion*:***
  - Hydrocodone combination products have a high potential for abuse, similar to oxycodone products which is a C-II substance
- **OSE Conclusion*:***
  - Hydrocodone combination products have lower rates of abuse compared to oxycodone products *(when a more appropriate denominator is used),* for measures of morbidity and mortality
  - Hydrocodone combination products are widely abused – but no objective threshold exists for determining scheduling

DEA and OSE: Main Findings

- **DEA Conclusion*:***
  - Non-narcotic active ingredients added to hydrocodone combination products (e.g., acetaminophen) do not reduce abuse potential
- **OSE Conclusion*:***
  - DEA presented no data to support this statement
  - Data from other products suggest abuse is lower for combination products than for single ingredient products

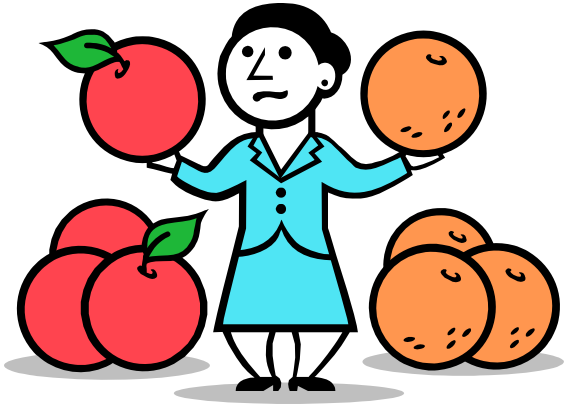
How do we quantify and compare abuse between products?

- No national abuse surveillance system for pharmaceutical products
- Abuse ratios (“abuse rates”) are computed to estimate risk of abuse in the population and compare between products
- Numerators and denominators come from separate data sources
- These estimates are crude, but they are the only measures currently available

Abuse-related Health Outcome Ratios: *Challenges*

- **Numerators – limited in granularity of data**
  - Morbidity & Mortality related to abuse
    - Drug Abuse Warning Network (DAWN)
    - National Poison Data System (NPDS)
    - Florida Department of Law Enforcement Medical Examiners (FDLE)
  - Reported Behaviors of abuse
    - National Survey on Drug Use and Health (NSDUH)
    - Monitoring the Future (MTF)
- **Denominators – no ideal one**
  - DEA and OSE differ on most appropriate choice
  - Choice of appropriate denominator is key
- **Comparator – oxycodone (C-II)**
  - Different formulations/compositions

Comparator



Hydrocodone Products

- All are combination products
- All products are immediate release
- Highest available tablet strength is 10 mg of hydrocodone

Oxycodone Products

- Composition & Formulation:
  - Combination products
  - Single Ingredient
    - Immediate Release (IR)
    - Extended Release (ER)
- Highest available tablet strength is 80 mg oxycodone (ER)

Hydrocodone vs. Oxycodone - Similarities

- Both hydrocodone and oxycodone:
  - Opioid analgesic
  - Single ingredient is schedule II substance under CSA
  - Approximately equipotent on a milligram basis as an oral analgesic
- The majority of both hydrocodone and oxycodone combination products contain acetaminophen
- Long marketing history
- Large market share

Hydrocodone vs. Oxycodone - Differences

- Composition and formulation type:
  - Single-entity vs. combination product
  - Immediate vs. extended release
- Clinical indications vary with formulation
- Average days of therapy per prescription
- Number of milligrams available per dosage unit

Percentage of *Total Number of Prescriptions* and *Total Amount of Substance Distributed* (sales in kg) for Hydrocodone and Oxycodone Containing Products in 2007 *

Product Name	% of Total Number of Prescriptions	*% of Total Amount Distributed (kg.)*
Hydrocodone		
○Single ingredient	<1	*<1*
○Combination	~100	*~100*
Oxycodone		
○Single ingredient	31	*73*
•*Immediate release*	*13*	-
•*Extended release*	*18*	-
○Combination	69	27

* *Data obtained from DEA Report:* IMS Health, Vector One®: National (VONA) , *Data Extracted September 2008.*

Numerators

Numerators are limited

- The majority of the existing drug abuse and diversion data sources **do not** provide information on:
  - specific product
  - composition (single ingredient vs. combination product)
  - formulation (immediate release vs. extended release)
- Key problem when examining **oxycodone products**; whereas hydrocodone products are ALL immediate release combination products

Numerator Data Sources
Morbidity

- **Drug Abuse Warning Network (DAWN)**
  - National Estimates of Drug Abuse Related Emergency Department visits
  - Substance, composition and formulation specific
- **National Poison Data System (NPDS)**
  - Calls to the Poison Control Centers
  - Provides information by substance only

Numerator Data Sources
Mortality

- **Florida Department of Law Enforcement Medical Examiners (FDLE)**
  - Drug related deaths in the state of Florida
  - Provides information by substance only

Numerator Data Sources

Self-Reported Behavior of Abuse

- **National Survey on Drug Use and Health (NSDUH) Data**
  - Provides national estimates on the non-medical use of pain relievers
    - Estimates of lifetime as well as first time users
    - Limited information by substance
- **Monitoring the Future (MTF) Data**
  - Provides data on drug taking behaviors of school attending adolescents
  - Provides data specific to Vicodin® and OxyContin® as well as other narcotics

Denominators

Infection by an agent is possible only if there is opportunity for exposure to the agent

-- Wade Hampton Frost (1880-1938)

Denominators – which one?

- **DEA Report**
  - Total U.S. population
  - Total Number of Prescriptions
  - **Patient-days of Therapy**
  - **Amount of Substance Distributed (in kilograms of the salt)**
- **OSE Review**
  - Total U.S. population
  - Total number of prescriptions
  - **Patient-days of Therapy**
  - **Amount of Substance Distributed (in kilograms of the salt)**
  - **Total number of patients receiving a prescription**
  - **Total number of tablets dispensed ("extended units")**

Total Number of Prescriptions

- **Assumption**: 

= 

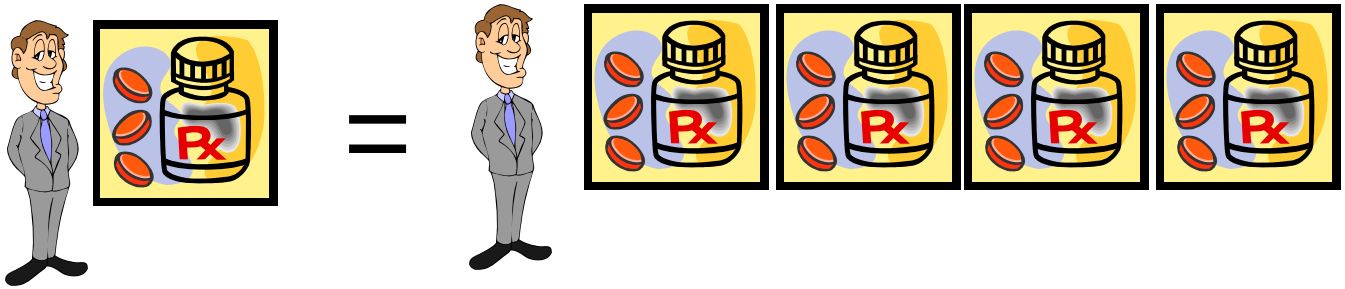
  1 Prescription of Hydrocodone = **1 Prescription of Oxycodone**

- **Strength**: adjusts for drug utilization

- **Limitation**: number of tablets, vary by prescription

Total Number of Patients

- **Assumption**:



- **Strength:** it approximates how many people are initially exposed to the drug product
- **Limitation**: the number of prescriptions per patient varies considerably by product

Total Patient-days of Therapy (TPDT)

= total days' supply added across prescriptions

- **Assumption:** TPDT will account for differences in duration of therapy between prescriptions
- **Strength:** accounts for some differences in days' supply between prescriptions
- **Limitation:** does not account for differences in dosage and thus the amount of tablets per prescription, which varies by product type

Total Kilograms of Drug Product

- **Assumption:** Sales from manufacturers to distributors account for all products sold into the marketplace
  - One kg hydrocodone exposure opportunity = one kg oxycodone exposure opportunity
- **Strength**:
  - Includes drug lost from supply chain prior to prescription, in transit and at the wholesalers
  - Includes drug diverted from pharmacies, hospitals, and physicians' offices
- **Limitation**: One kilogram of hydrocodone yields many more dosage units (e.g. tablets) than one kilogram of oxycodone

Calculated Number of Tablets per Kilogram: *Hydrocodone, Oxycodone Products*

Opioid	Equianalgesic Dose to Morphine 15 mg	Strengths Available	Number of Tablets/KG (Based on weighted average of all dispensed doses)
Hydrocodone /APAP	15 mg	2.5 to 10 mg	141,000
Oxycodone IR, ER, combination	10 mg	2.5 to 80 mg	77,000

Total Number of Tablets Dispensed

= Number of tablets ("extended units") dispensed from pharmacies

- Assumption: Each "extended unit" or tablet is an "exposure opportunity" and represents drug availability for abuse
- Strength: Accounts for variability due to number of tablets per prescription and days of therapy; formulation and composition
- Limitation: Does not account for drug diverted from supply chain

Need denominator that accounts for most differences between products

- **DEA current thinking:**
  - **Sales of drug product in kilograms**
    - Does account for drug lost from supply chain prior to prescription
    - Does not account for any of prescribing, composition and formulation differences
- **OSE current thinking:**
  - **Total tablets (extended units) dispensed**
    - Does account for some prescribing, composition and formulation differences between products
    - Does not account for drug lost from supply chain prior to prescription

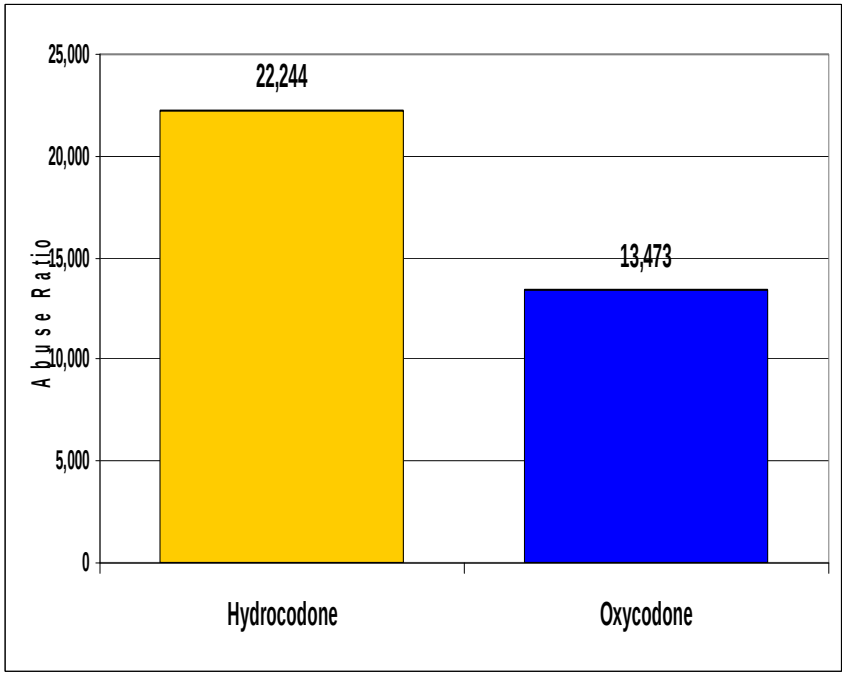
Results

Confidence Intervals

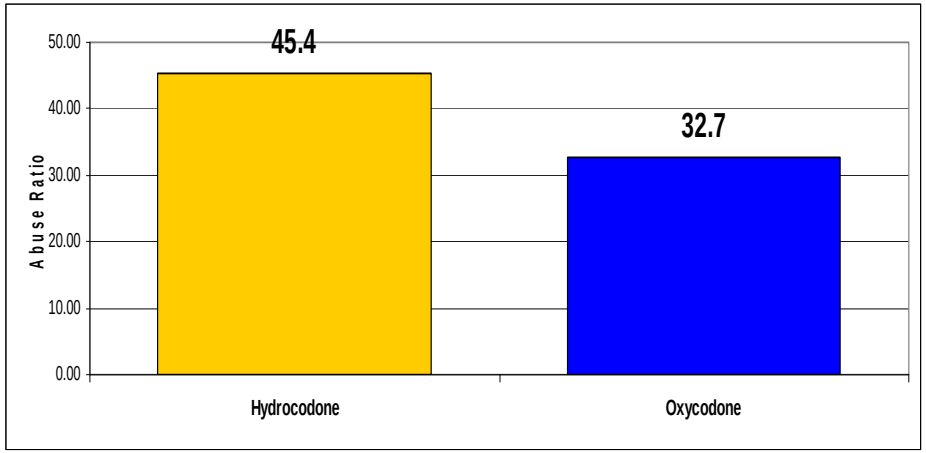
- Sources for numerators and denominators are derived using different sampling methodologies and populations
  - Confidence Intervals on rates of drug abuse-related outcomes cannot be computed
  - Statistical testing cannot be conducted

Abuse Ratios: Poison Control Calls 2006

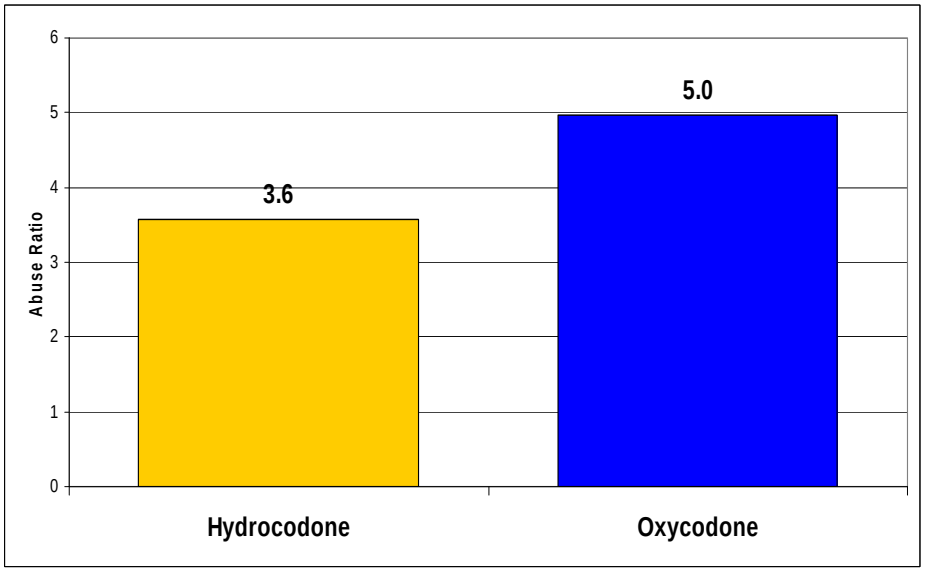
Denominator = US Population



Denominator = 100 Kgs Sold



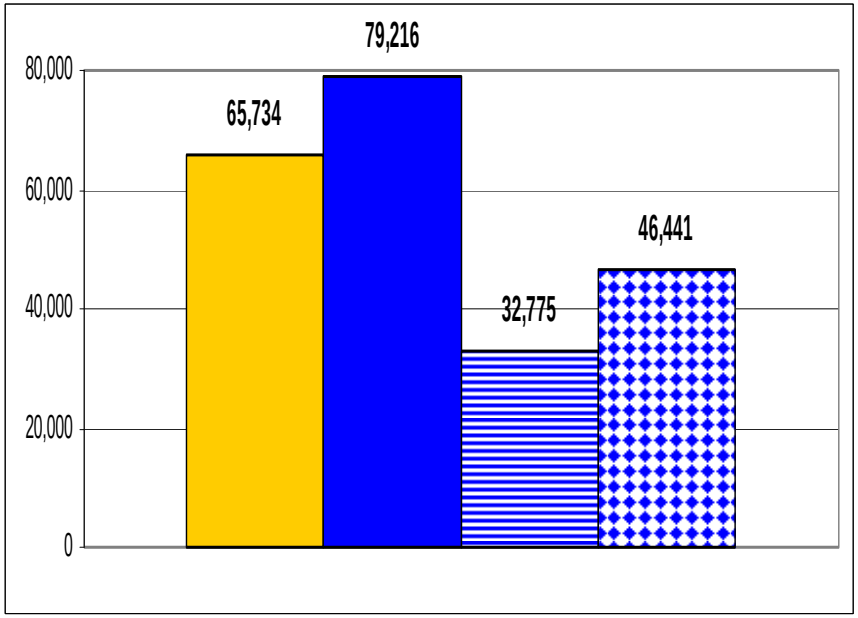
Denominator = Million Tablets Dispensed



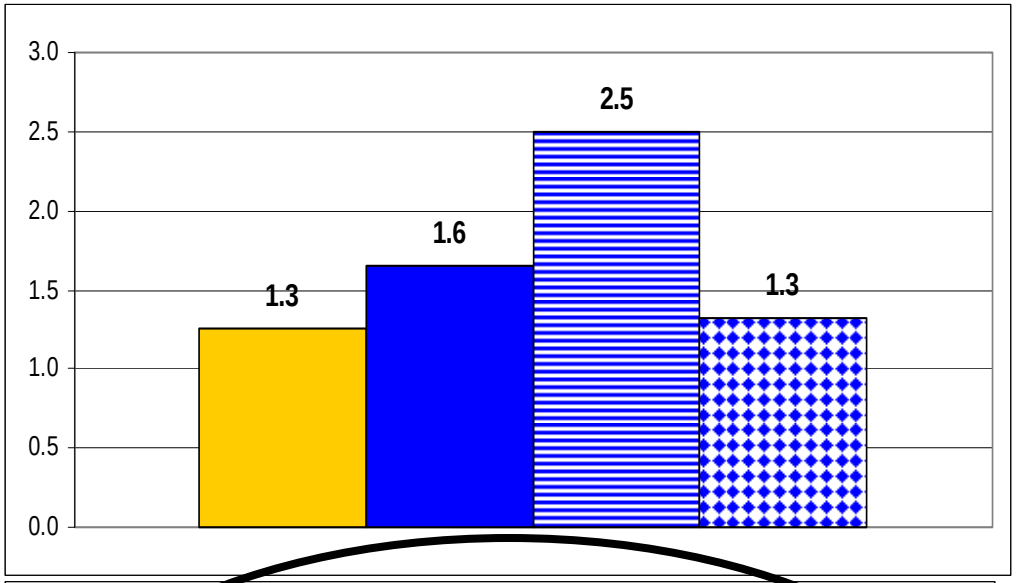
Data obtained from DEA Report
Extended Units from: IMS Health, Vector One®: National (VONA), Data Extracted September 2008.

DAWN Data Analyzed with Various Denominators – 2007

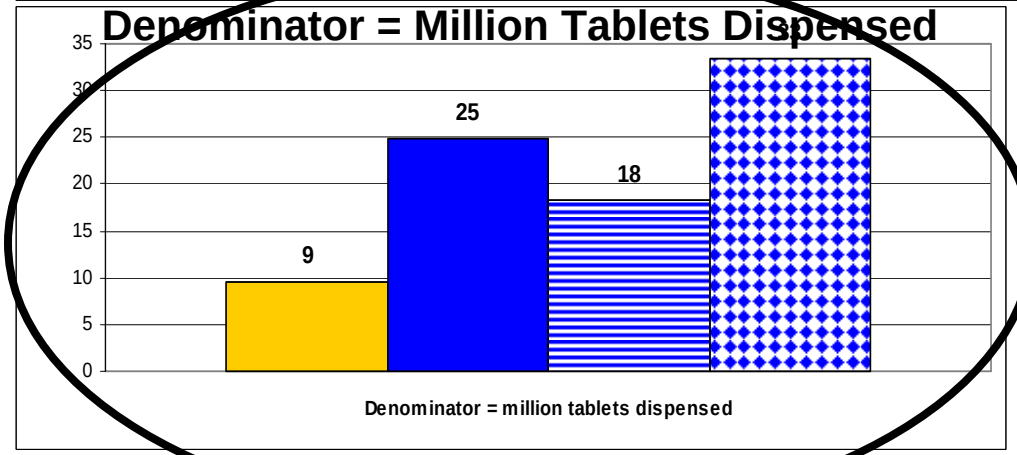
Denominator = US Population



Denominator = 100 Kgs Sold



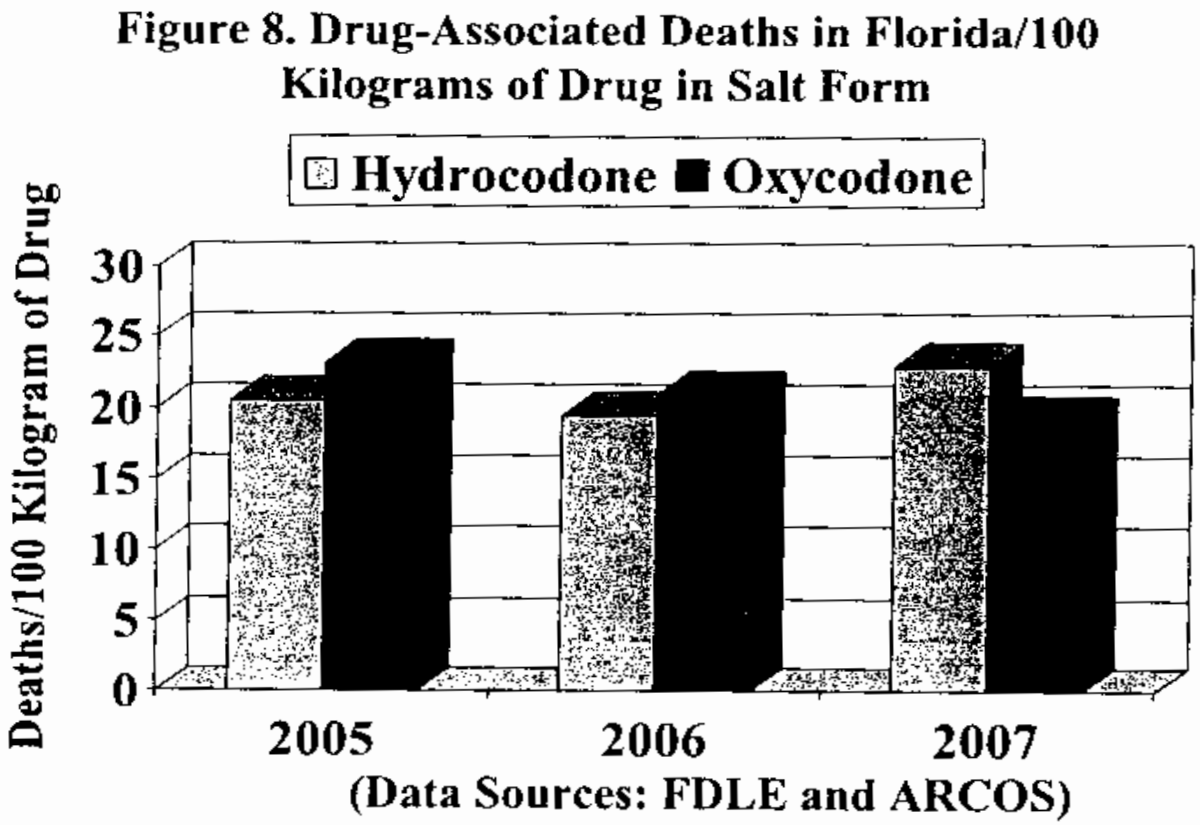
Denominator = Million Tablets Dispensed



- Hydrocodone abuse related ED visits
- Oxycodone abuse related ED visits
- Oxy combination abuse related ED visits
- Oxycodone single entity abuse related ED visits

*OSE Analysis. *Sources: Center for Behavioral Health Statistics and Quality, SAMHSA,;* IMS Health, Vector One®: National (VONA) . *Extracted 9/08*

DEA's Analysis of FDLE Data



National Survey on Drug Use and Health (NSDUH)

Year	Ratio of Past Year Initiates of Hydrocodone Combination Products and Oxycodone Products per Million Tablets Dispensed, 2002-2005*	
	Hydrocodone	**Oxycodone**
2002	0.35	0.31
2003	0.33	0.28
2004	0.28	0.31
2005	0.24	0.20

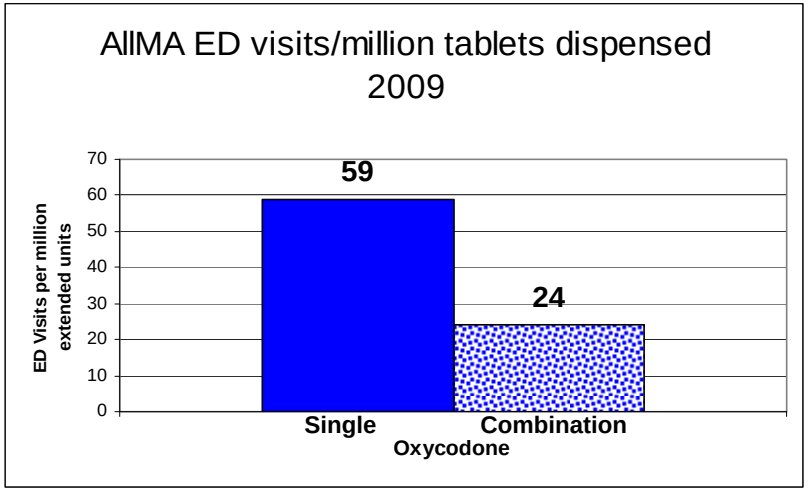
**OSE Analysis. Sources: Center for Behavioral Health Statistics and Quality, SAMHSA, National Survey on Drug Use and Health;* IMS Health, Vector One®: National (VONA) . *Extracted 9/08*

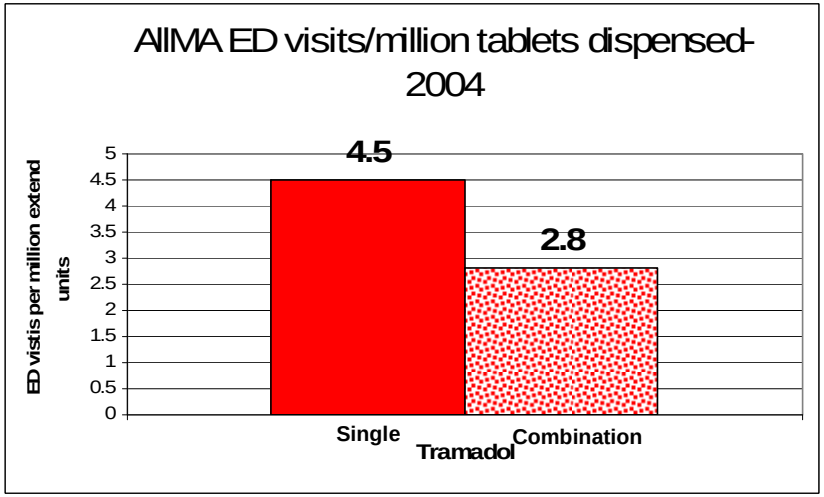
Monitoring the Future

- Higher **prevalence** of use of hydrocodone combination products (Vicodin®) than oxycodone products (OxyContin®) among high school students
  - More prescriptions – more availability in homes
  - Cannot link reported use with measures of morbidity and mortality

No data to support DEA assertion: Adding acetaminophen to hydrocodone does not deter abuse

- ***DEA Conclusion: Non-narcotic active ingredients added to hydrocodone combination products (e.g., acetaminophen) do not deter this abuse potential***
- No single-ingredient hydrocodone product for comparison
- Oxycodone and tramadol
  - DAWN data
  - Combination products are abused less than single-ingredient products





**OSE Analysis. Sources: Center for Behavioral Health Statistics and Quality, SAMHSA,;* IMS Health, Vector One®: National (VONA) *. Extracted 1/11.*

Conclusions

- Crude “abuse ratios” can be used to characterize abuse risk of hydrocodone, compared to schedule II products
- Oxycodone combination products are most appropriate comparators
- Abuse ratios are highly dependent on the numerator and denominator
  - **Numerator** = DAWN (most granular)
  - **Denominator** = Tablets dispensed (accounts for most differences between hydrocodone and oxycodone)

Conclusions

- Preponderance of data indicate that hydrocodone combination products have lower abuse ratios than oxycodone combination products (schedule II)
  - Despite much larger prescription volume/availability
- Data do not support DEA's assertion that non-narcotic active ingredients in hydrocodone combination products do not reduce the abuse potential of hydrocodone
  - Indirect evidence from other products suggests the opposite
- Data suggest that hydrocodone combination products are widely abused