FDA Analysis of Long-Term Trends in Prescription Opioid Analgesic Products: Quantity, Sales, and Price Trends

March 1, 2018

Introduction

To provide improved understanding and support Agency efforts to address the current opioids crisis, we have assembled a dataset of sales and quantities of retail prescription opioid analgesics sold spanning 25 years. This report summarizes data and methods that we use to evaluate the trends in sales, volume, and prices of prescription opioid analgesics over time.

Definitions of the retail prescription opioids analgesic market

The complexity of opioid risks, such as with misuse, abuse, addiction, overdose and death and the increasing rates at which they are occurring, all contribute to the significant public health burden of the opioid epidemic. Opioid products dispensed for outpatient use may be more likely to be misused and abused than opioid products used in the inpatient setting.[1] This may be due to greater availability and easier access and the difference in healthcare provider oversight in outpatient settings compared to inpatient settings. For example, for years 2012-2016, sales data, measured in dollars, of products sold from manufacturers to pharmacies and other settings of care show that sales to the retail setting accounted for the majority of annual opioid analgesic sales (>80%) and injectable formulations accounted for less than 0.2% of those sales.[2] Therefore, this analysis focuses on sales to the retail setting and includes all formulations of opioid analgesics except for injectable formulations, which are not commonly dispensed in an outpatient setting. Additionally, we focused on opioid analgesic products for the purposes of this analysis; opioid-containing products used as part of medication-assisted treatment (MAT) for opioid dependence and opioid-containing cough/cold products are not included in our analysis because of their different indications and patterns of use.

Results

Quantity

Quantities of analgesic opioids, as measured in morphine milligram equivalents (MMEs) sold from manufacturers to retail pharmacies gradually increased from nearly 50 billion MME in 1992 to about 73 billion MME in 1998, increased more steadily in 1999 – 2000 to 92 billion MME, and then rapidly increased by an average rate of more than 15 billion MMEs per year for the next decade, peaking at nearly 250 billion MME of opioids sold in 2010 (figure 1). Over the entire timeframe, generic versions of opioids were available for many of the opioid products on the market, and comprised most of the MMEs sold to pharmacies over the entire timeframe studied. The generic share of MMEs has steadily increased in the most recent timeframe with generics comprising 53% of MMEs sold in 2000, and rising

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[1]Notification letters for the expansion of the Extended-release and long-acting opioid analgesic REMS https://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm305245.htm.

[2] IQVIA National Sales Perspective (NSP). 2012-2016; extracted January 2018.

to account for over 90% of MMEs sold in 2016. Overall prescribing trends have similarly shown increased dispensing rates for generic drugs, including non-opioid drugs, during this interval.[3]

Figure 1: Total MMEs sold for aggregate opioid analgesic market – by brand / generic
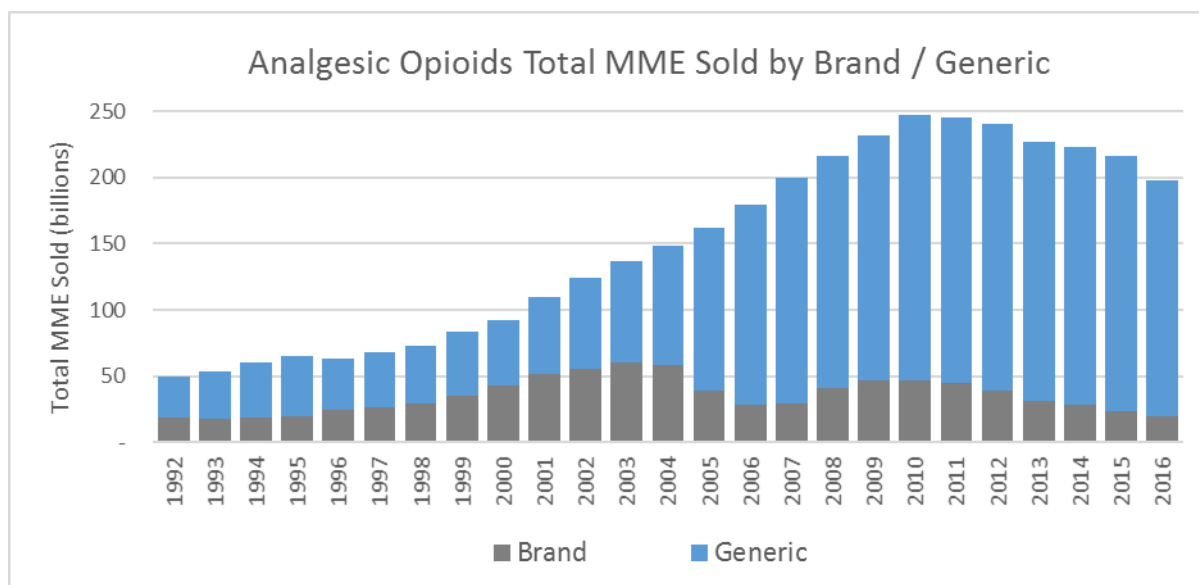
The rapid uptake of opioids sold was primarily produced by a few key active moieties: oxycodone, hydrocodone, fentanyl, morphine, methadone, and tramadol (figure 2).   Of these, oxycodone, hydrocodone, fentanyl, and morphine products, which comprised less than 25% of MME sold in 1992, grew to account for over 80% of MME sold by 2011. Propoxyphene, which is no longer marketed, comprised the majority of opioids MME sold between 1992 and 1995. Sales of propoxyphene products had gradually declined over time, until its removal from the US market in 2010 because of serious heart risks associated with its use.

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[3] Generic Pharmaceutical Association Annual Report 2014;
http://www.gphaonline.org/media/wysiwyg/PDF/GPhA2014AnnualReport.pdf

Figure 2: Total MMEs sold for aggregate opioid analgesic market – by active moiety
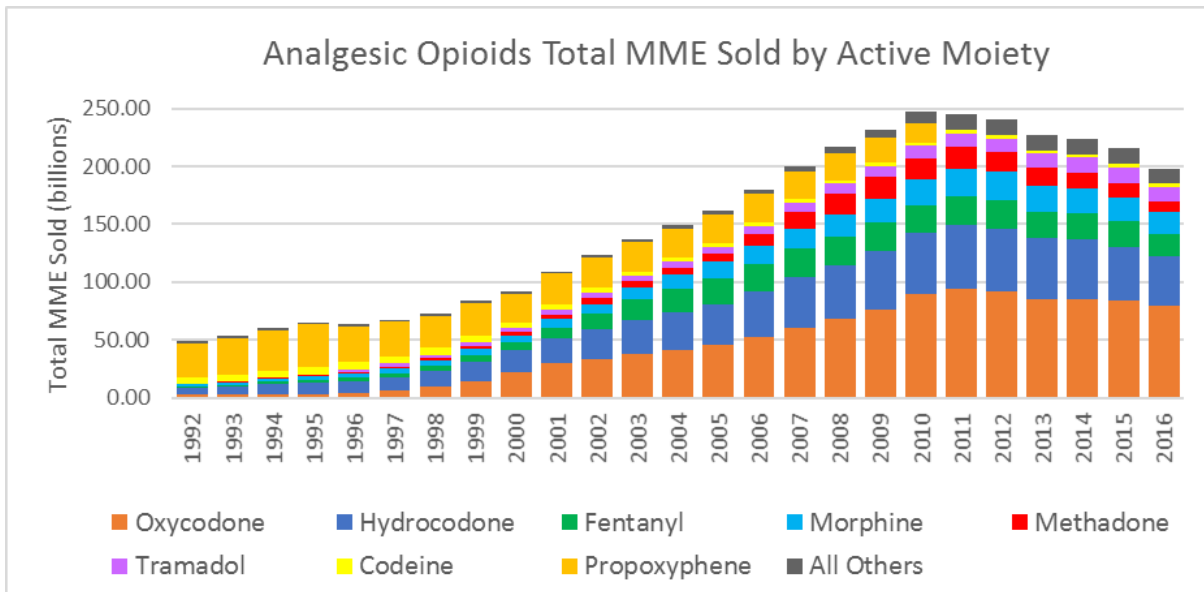
Within these active moiety groupings, it is important to note that most of these opioids are marketed under multiple formulations, including immediate-release and extended-release versions as well as opioids in combination with other analgesics such as acetaminophen. To evaluate these aggregate trends at a more granular level, we identified specific products (i.e., the opioid active moiety and/or other analgesic, and the formulation, but not the strength), which comprised most MMEs sold for each opioid. (figure 3)

**Figure 3: Total MME Sold for Leading Opioid Products**
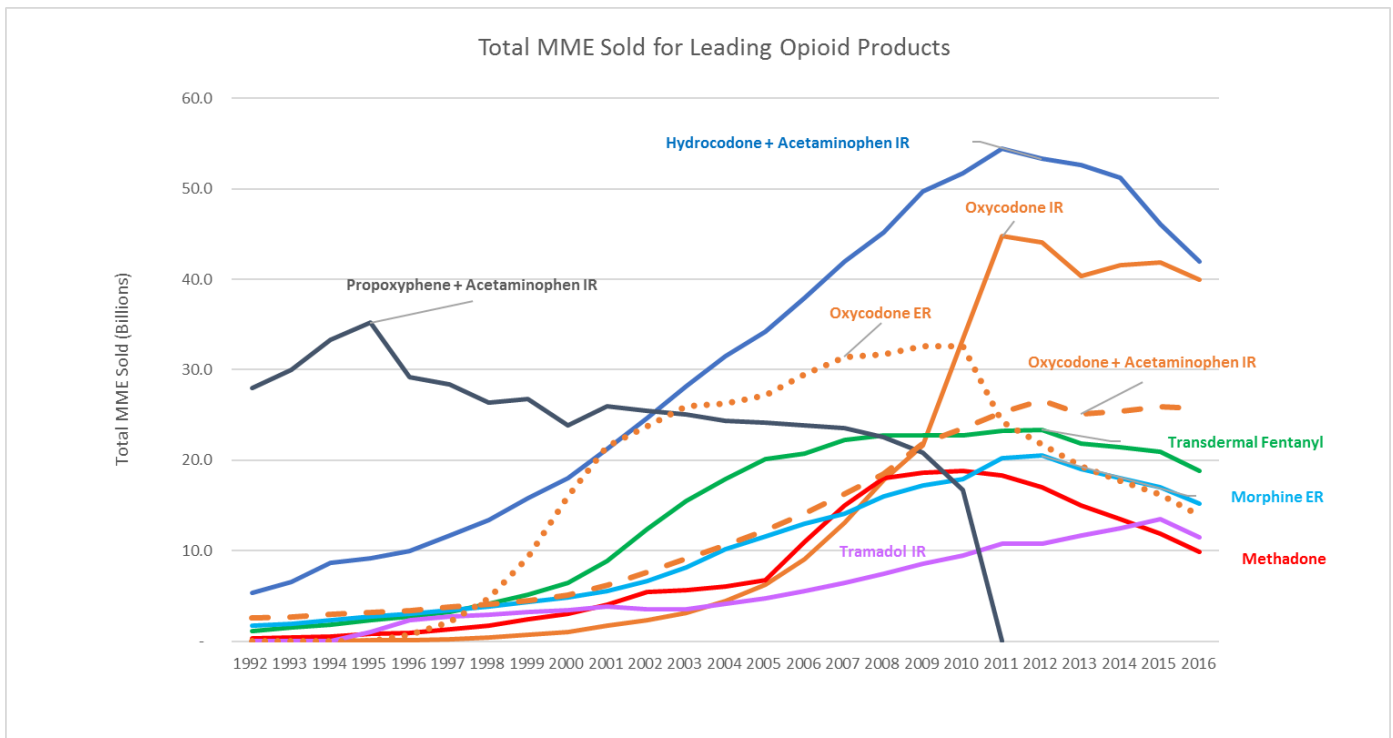
Particularly notable in figure 3 are the differences in the rates of change in quantities sold (in MME) of these different products and in the dates for the peak quantities sold, which precede 2016 for all products with the (apparent) exception of Oxycodone + Acetaminophen IR relative to the overall aggregate trends in opioid MME observed in figure 1. Changes in the annual total of morphine milligram equivalents sold may be due to a number of factors such as drug product, dosage, strength, or quantities ultimately prescribed and dispensed; further investigation is necessary to fully understand the complex factors contributing to these pattern changes over time.

Sales and Prices

We also evaluated total sales and quantities sold in MME to calculate average annual prices per MME for these products to see if any clear relationship between prices and sales volume were present. It is important to point out that the sales measures provided by IQVIA represent invoice prices that pharmacies pay to manufacturers and drug wholesalers, and not prices paid by patients or insurance providers. The price measure is interpretable as an average price per unit of analgesic relief, and is not the price of the pharmaceutical product per se. Unlike the standard price indices used by economists to measure the average price level of sundry goods, the measure $ / MME provides an interpretation based on equivalent analgesic effects across various opioid active moieties.

The retail opioid market had grown dramatically over this timeframe, from less than $1 billion in sales in 1992, peaking at $8 billion dollars in 2015 (Figure 4). Oxycodone and fentanyl products, which had combined retail sales of less than $150 million in 1992, accounted for $5 billion dollars in sales and over 70% of the retail opioid market share by 2009.

Figure 4: Combined Retail Sales of Analgesic Opioid Products
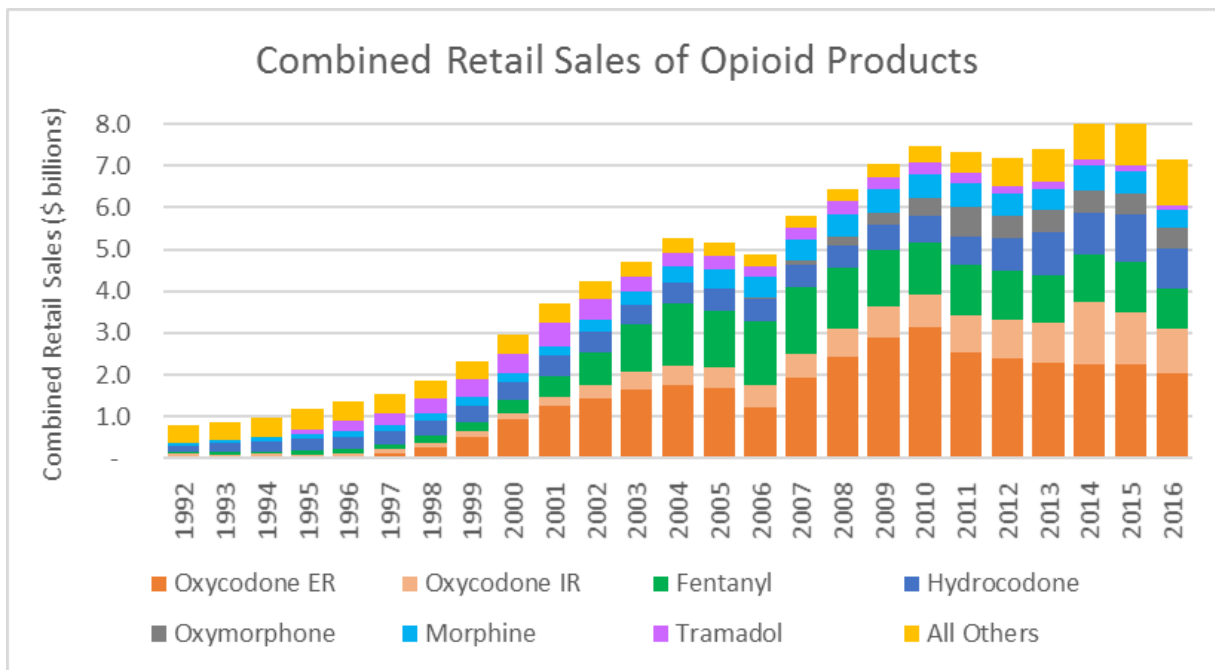
As shown in Figure 5a, the average price of retail analgesic opioids rose significantly from about 1993 to 2000. It then plateaued until 2004 before dropping to a new lower level for the years 2004 to 2005.

This trend shows no clear relationship with the total prescription retail analgesics sold as measured in MME.

Figure 5a: Total MMEs Sold and Price per MME for Aggregate Opioid Analgesic Market
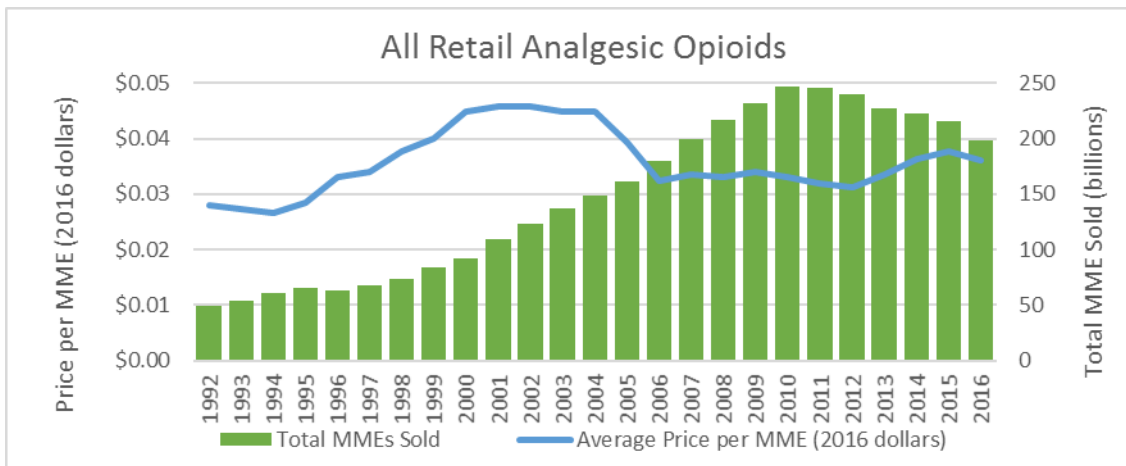

We also decomposed average price by brand and generic version (figures 5b and 5c) and similarly find no clear price / quantity relationships, with prices for both brand and generic products generally increasing over time. The average price for generic opioids were found to be less than 2.5 cents per MME over the entire timeframe, while average brand prices ranged from roughly 6 cents per MME in 1992 to 12 cents per MME in 2012. Beginning in 2013, branded prices increased more sharply to 20 cents per MME in 2016.

**Figure 5b: Total MMEs Sold and Price per MME for Brand Opioids**
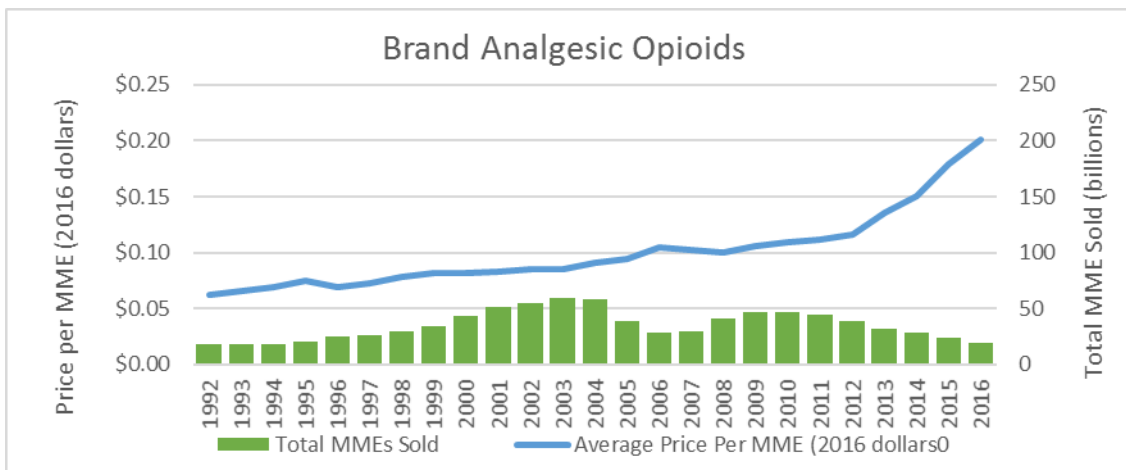
Figure 5c: Total MMEs Sold and Price per MME for Generic Opioids
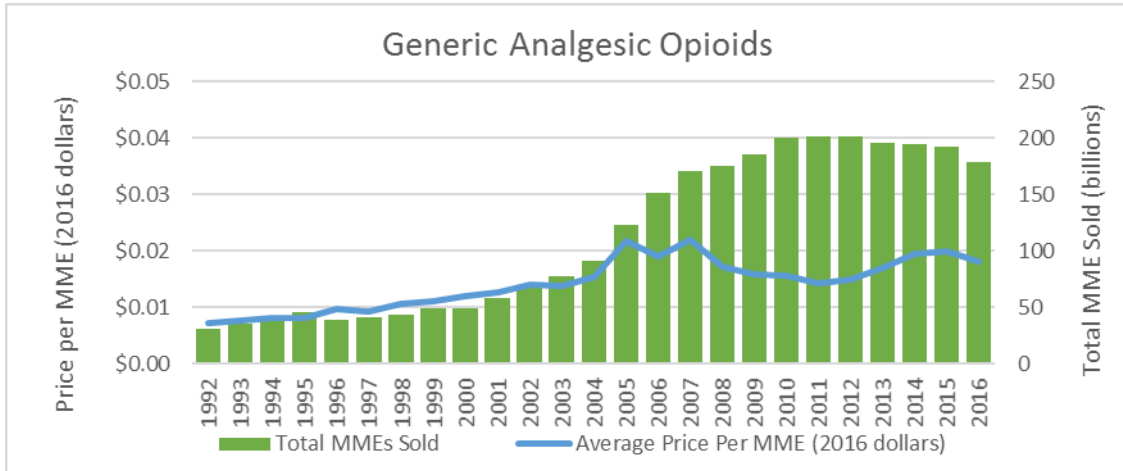
Although no price / volume relationships are observable in the data, we do find that products having a lower price per MME tend to do well relative to higher-priced products. (Figure 6). In 1992, 78% of MMEs sold were for products with an average price of less than 5 cents per MME, with this ratio steadily declining to 59% by 2002. Beginning in 2003 that trend reversed and has steadily increased with 85% of MMEs sold in 2016 coming from products with an average price below 5 cents per MME.

Figure 6: Proportion of MMEs Sold by Average Price
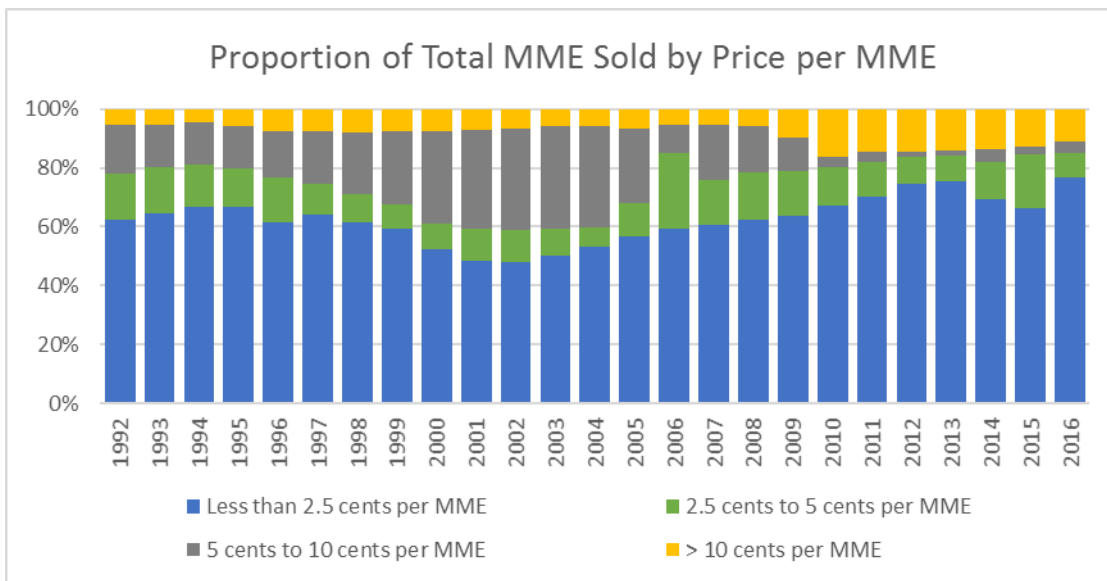
Formulation Trends

We also evaluated these data to quantify trends in use of abuse-deterrent formulations of opioid products. These formulations are intended to make certain types of abuse, such as crushing a tablet to snort or dissolving a capsule to inject, more difficult or less rewarding. For the purposes of our analysis we only included products which have received FDA-approved abuse-deterrent labeling. The science of

abuse deterrence is relatively new, and we evaluated these trends beginning in 2011 and found very low uptake of these new products, with only 5-6% of MMEs sold during that timeframe coming from ADF-formulated opioids.   In 2016 the average price per MME for ADF formulated opioids was roughly 15 cents per MME, compared to only 3 cents per MME for non-ADF opioid products. There are currently no generic opioids with FDA-approved abuse-deterrent labeling.

Figure 7: Proportion of MMEs that are for Abuse Deterrent Properties
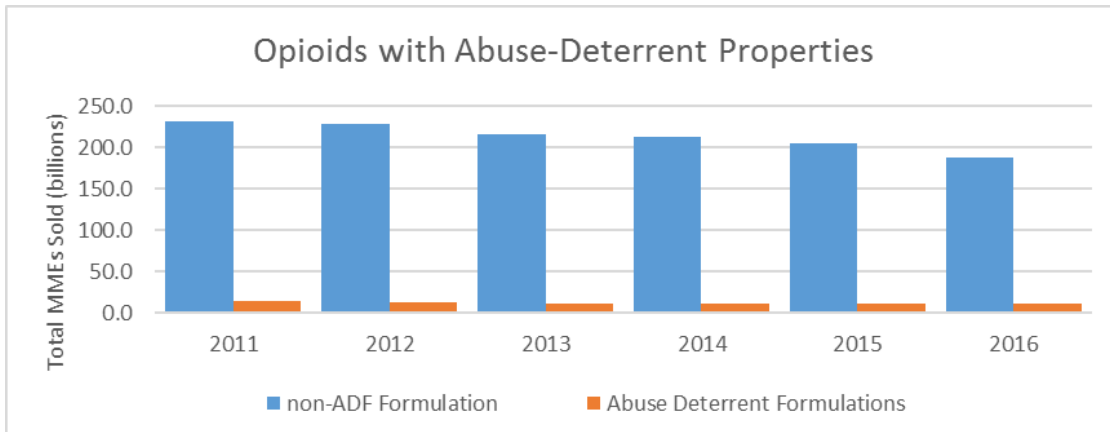
We also analyzed trends in MMEs sold for both immediate release (IR) opioids and extended release/long acting (ER/LA) opioids (Figure 8a and 8b).   From 1992 – 2010 the quantity of MMEs sold for both IR and ER/LA opioids increased dramatically. However, during that timeframe, ER/LA opioids which comprised only 7% of MMEs sold in 1992, accounted for 1/3 of MMEs sold in 2000, and over 40% of MMEs sold by 2003 (figure 8c).   While MMEs for ER/LA products began to decline in 2010, the decline in the quantity of IR MMEs did not begin until 2013. Over 60% of the roughly 50 billion MME decrease in MMEs sold observed from 2010 – 2016 are from decreased sales in ER/LA products.

Figure 8a: Total MMEs sold for Immediate Release (IR) Opioids
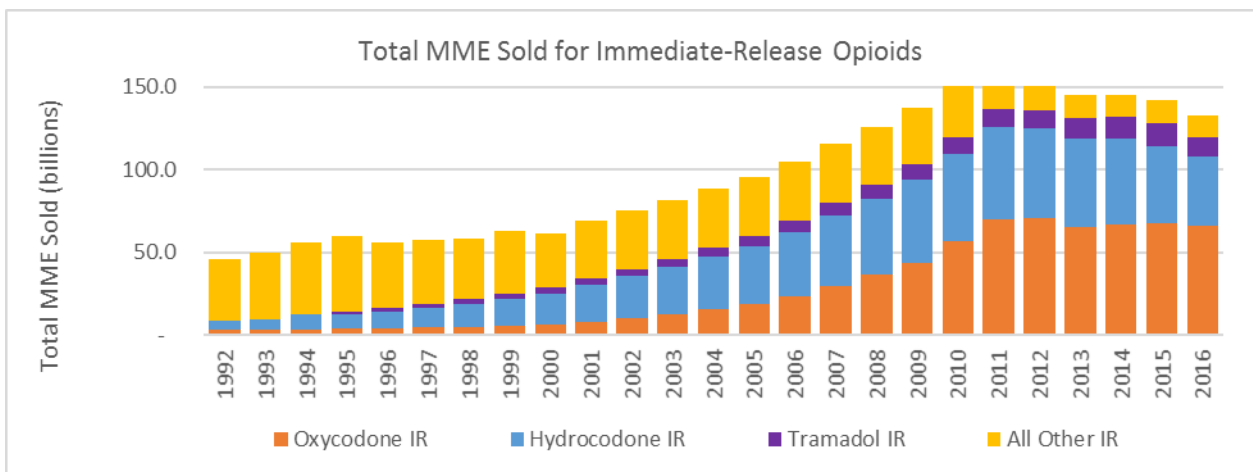
Figure 8b: Total MMEs sold for Extended Release / Long-Acting (ER/LA) Opioids

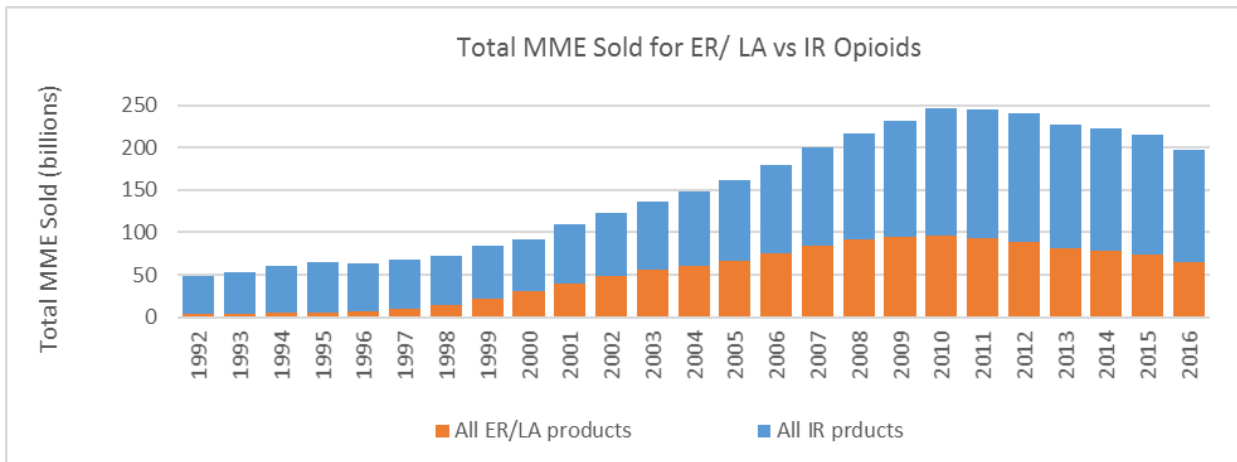Total MME Sold for Extended Release / Long-Acting Opioids

Legend: Oxycodone ER, Fentanyl Transdermal, Morphine ER, Methadone, All Other ER / LA
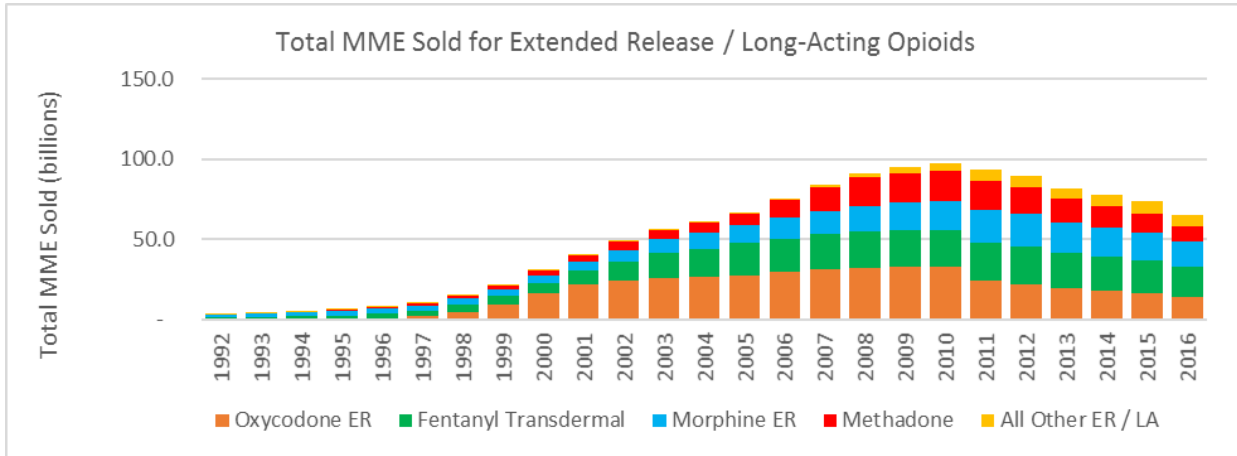
Figure 8c: Total MMEs sold by IR and ER / LA

Total MME Sold for ER/ LA vs IR Opioids

Legend: All ER/LA products, All IR prducts

Appendix:

Key characteristics of the IQVIA data file for the retail opioid analgesics market

Data was extracted from the IQVIA, National Sales Perspectives™: Retail and Non-Retail Database.

The IQVIA National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, "eaches", which may be interpretable as bottles of pills, extended units, which may be interpretable as number of pills, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, and food stores.

Data were provided from 1992 – 2016 for all retail analgesic opioids grouped by molecule, formulation, manufacturer, and strength. Brand and generic drug identifiers were also provided. Annual measures of extended units sold and total sales dollars were provided for each product. The definitions of these variables are provided below.

Definitions of key IQVIA variables

Sales$

This variable is a measure of the amount of money non-retail and retail outlets spent on a drug product acquired from manufacturers and drug distributors/wholesalers based on the outlet's invoice for bulk order purchasing, since 1992.

Combined Molecule

This variable identifies products with a unique molecule or combination of molecules.

Strength

This variable identifies the different potencies or strengths. These are expressed in different ways depending on the presentation of the product, for example milligrams for oral tablets and capsules, milligrams per milliliter for oral and injectable liquids, micrograms per hour for transdermal products, and such.

Brand/Generic

This data element classifies products by their status as brand, generic, branded generic, or other, as classified by IQVIA. It enables identification of products by this status and reports on totals and trends for brand and generic products in a particular market.

Overall, this classification of products may differ from FDA's standard terminology based on whether a product approval derived from a New Drug Application or an Abbreviated New Drug Application (ANDA). IQVIA appears to classify all trade name products as brand or branded generic. "Generic" products appear to include only those products with no trade name. Products approved as NDAs and ANDAs are classified as "brand" prescriptions if they have a trade name, while prescriptions for products with no trade name, including some approved as NDAs are defined by FDA as "generic" prescriptions.

Extended units are the number of tablets, capsules, milliliters, ounces, etc. of a product shipped in each unit. Extended often are not meaningful above the package level, because a product may have different forms and strengths and, therefore, a different type of unit for each presentation.

This data element refers to the physical dosage form of a drug, such as oral or injectable. This system consists of three levels, with each successive level containing more detail about the product form. For example:

Product Form 1 = O contains all orals

Product Form 2 = OL contains all oral liquids

Product Form 3 = OLS contains all oral liquids in syrup form

Our data captures opioid products at the more granular product form 3 level.

Limitations of these data

Numerous metrics are not available consistently for the types of historical data we were seeking. In addition, IQVIA made changes to the underlying source data and projection methodologies over time. Therefore, our analysis focused on data for the variables and metrics available consistently from 1992-2016 in a form that allowed for the calculation of a prices based on morphine milligram equivalents (MME) of the selected opioid analgesics. Of note, National Drug Code (NDC) product identifier data are not available historically back to 1992, therefore we used product formulation and strength of molecules to calculate MME based on the volume of extended units sold.

Findings from this review should be interpreted in the context of the known limitations of the databases used. These data do not provide a direct estimate of use but do provide a national estimate of units bought by retail outlets from distributors and wholesalers through the U.S. pharmaceutical supply chain. Sales of products outside of the supply chain are not captured, for example illicit sources of opioids such as fentanyl. The amount of product purchased by these channels of distribution may be a reasonable surrogate for use, if we assume the facilities purchase drugs in quantities reflective of actual patient use, i.e., that waste or diversion is constant or negligible.

Standardization of data using morphine milligram equivalents (MME)

Morphine is often used as the reference point for other opioids. The CDC developed a conversion reference table that contains MME conversion factors for opioid medications, organized by molecule and National Drug Code (NDC). The table contains all the fields necessary to compute the MMEs.   A summary table of opioid MME conversions is provided in Table 1.

Table 1: Opioid Morphine Milligram Equivalent (MME) Conversion Factors[4]

Type of Opioid (strength units)	MME Conversion Factor
Buprenorphine film/tablet (mg)	30
Buprenorphine patch (mcg/hr)	12.6
Buprenorphine film (mcg)	0.03
Butorphanol (mg)	7
Codeine (mg)	0.15
Dihydrocodeine (mg)	0.25
Fentanyl buccal or SL tablets, or lozenge/troche (mcg)	0.13
Fentanyl film or oral spray (mcg)	0.18
Fentanyl nasal spray (mcg)	0.16
Fentanyl patch (mcg)	7.2
Hydrocodone (mg)	1
Hydromorphone (mg)	4
Levorphanol tartrate (mg)	11
Meperidine hydrochloride (mg)	0.1
Methadone (mg)	3
Morphine (mg)	1
Opium (mg)	1
Oxycodone (mg)	1.5
Oxymorphone (mg)	3
Pentazocine (mg)	0.37
Tapentadol (mg)	0.4
Tramadol (mg)	0.1

For all products in our dataset, the opioid component and corresponding extended unit (tablet, capsule, milliliters of liquid, transdermal patch, lozenge, spray, etc.) were identified, along with the strength, strength unit (mg for most oral dosage forms, mcg or mcg/hr for other presentation such as transdermal patch, spray, lozenge, etc.). For all products and presentations, we expressed all strength units from the IQVIA data in terms which directly corresponded with the strength units in the MME conversion reference table. We then calculated the quantity of MMEs sold per product per year by multiplying opioid strength times the MME conversion factor times the total number of extended units sold in each calendar year.

Sales and Pricing

IQVIA data provide total annual purchases by retailers from manufacturers and wholesalers and distributers for each product. For each product, the average price per MME is calculated by dividing

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[4] Source: CMS.gov for additional details see: https://www.cms.gov/Medicare/Prescription-Drug-Coverage/PrescriptionDrugCovContra/Downloads/Opioid-Morphine-EQ-Conversion-Factors-Aug-2017.pdf for more technical details on calculating MMEs see: http://www.pdmpassist.org/pdf/BJA_performance_measure_aid_MME_conversion.pdf

total annual sales by total annual quantity of MMEs sold as described above, thus prices are expressed as an average annual price per MME.

We convert prices to constant 2016 dollars using the BLS Consumer Price Index for All Urban Consumers (CPI-U)

Summary Data on Price and Volume:

Year	Total MME Sold (billions)	Price Per MME (2016 dollars)
1992	49.3	$ 0.028
1993	53.7	$ 0.027
1994	60.5	$ 0.027
1995	65.5	$ 0.029
1996	63.6	$ 0.033
1997	67.7	$ 0.034
1998	73.1	$ 0.038
1999	84.0	$ 0.040
2000	92.1	$ 0.045
2001	109.3	$ 0.046
2002	123.7	$ 0.046
2003	137.2	$ 0.045
2004	148.9	$ 0.045
2005	161.5	$ 0.039
2006	179.5	$ 0.032
2007	200.0	$ 0.034
2008	216.7	$ 0.033
2009	232.1	$ 0.034
2010	247.3	$ 0.033
2011	245.7	$ 0.032
2012	240.5	$ 0.031
2013	226.8	$ 0.034
2014	223.2	$ 0.036
2015	215.8	$ 0.038
2016	198.0	$ 0.036