Testimony of

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Hearing on "Treating the Opioid Epidemic: The State of Competition in the Markets for Addiction Medicine"

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Good afternoon Chairman Marino, Ranking Member Johnson, and the Members of the Subcommittee:

My name is Anne Pritchett, Vice President, Policy and Research, at the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading innovative biopharmaceutical research companies, which are devoted to developing medicines that enable patients to live longer, healthier and more productive lives. Since 2000, PhRMA member companies have invested more than half a trillion dollars in the search for new treatments and cures, including an estimated $58.8 billion in 2015 alone.

I have spent a substantial portion of my career focused on substance abuse issues including almost 8 years in the Office of National Drug Control Policy before joining PhRMA. The adverse health effects of the misuse of prescription opioids, including abuse, dependence, and overdose are a well-documented public health crisis. According to the Centers for Disease Control and Prevention, the rate of deaths from drug overdoses has increased 137%, including a 200% increase in the rate of overdose deaths involving opioids (opioid pain relievers and heroin) since 2000. [i] The total economic burden related to the abuse of prescription opioids is estimated to be as high as $78.5 billion, which includes health care, substance abuse treatment, and criminal justice costs.[ii] Of course these statistics do not begin to fully consider the impact on families and communities across the country nor the challenges and suffering of individuals seeking to break the cycle of addiction. Given the growing toll related to the abuse of prescription opioids and heroin, we must collectively redouble our efforts to prevent the misuse, abuse, and diversion of prescription medicines. While more than 90 percent of the prescription medicines most susceptible to abuse are generic,[iii] PhRMA and its members are committed to supporting the appropriate use of prescription medicines and working with others to collectively address the growing problem of opioid abuse and addiction.

I am pleased to appear before you to provide PhRMA's perspective on the critical issue of prescription drug abuse and medications to help prevent overdose and treat addiction. Our Industry is committed to the research and development of new therapies, including the development of non-opioid analgesics, abuse deterrent formulations (ADFs) of medicines that are intended to help prevent abuse, and various medicines to treat addiction and prevent overdose.

Today, I will briefly speak to the following areas:

- PhRMA's perspective on the overall policy framework for addressing opioid abuse
- Competition dynamics for medication assisted-treatments including opioid overdose reversal agents
- Current market for medication assisted treatments for overdose reversal
- Current market for other medication-assisted treatments for addiction

Policy Framework to Stop Opioid Abuse

We need a balanced approach that ensures appropriate access and use of prescription medicines by patients for legitimate medical needs under the direction and care of a licensed health care professional, but that also reduces the potential for misuse, abuse and diversion. Prescription drug abuse is a complex problem with no single solution—rather it requires a multi-pronged approach. To combat prescription drug abuse and particularly opioid abuse, PhRMA supports the following policies (for more detail, please see PhRMA's policy recommendations at http://www.phrma.org/policy-paper/for-a-healthier-america-strategies-to-combat-prescription-drug-abuse):

- *Expand education and training related to prescription drug abuse, pain management, and treatment options.* Physicians and other prescribers are often on the frontlines of the fight against prescription drug abuse. Prescribers need ongoing training to ensure they meet the legitimate medical needs of patients while reducing the potential for abuse, but increasingly first responders including friends and family are best positioned to assist an overdose victim. In addition to continuing to increase awareness of the dangers of prescription abuse and the signs of overdose and how to assist an overdose victim, public policies need to:

  - *Require ongoing prescriber education and training* to ensure appropriate prescribing of controlled substances, effective pain management, identification of patients at risk for prescription drug abuse and overdose, identification of those in need of treatment, and awareness of available treatment options.

  - *Foster the development and dissemination of evidence-based clinical guidelines* to inform opioid selection, dosage, duration, follow up, and discontinuation, including guidance on the <u>first opioid prescription</u> for patients for acute pain to ensure that no greater quantity than needed is prescribed for the expected duration of pain severe enough to require opioids. In considering initiation or continuation of opioid therapy, prescribers should be informed by evidence based clinical guidelines that include guidance on whether and under what circumstances a non-opioid analgesic, an abuse-deterrent formulation (ADF) (which makes the drug more difficult to abuse), or a non-medical treatment is appropriate.

- *Prevent and detect potential doctor shoppers.* One of the most promising tools in preventing and detecting potential doctor shoppers while allowing for legitimate medical use of needed prescription medicines by patients is Prescription Drug Monitoring Programs (PDMPs). These state-run data bases collect, analyze, and share dispensing information on controlled substances, providing critical information to providers to inform their prescribing. We support mandated training and use of PDMPs, efforts to expand the timeliness and quality of data included in these data bases, and efforts to increase interoperability and standardization of key elements to facilitate the generation of information to assist all prescribers in easily identifying potentially problematic behavior.

- *Encourage the development of ADF products, non-opioid pain medications, and medications to treat addiction and prevent overdose.* Despite ADF products' role in preventing widespread abuse by impeding delivery of the active ingredient, we continue to see non-ADF versions of the same drug on the market despite an ADF product being available. We encourage the FDA to use its existing authority to remove non-ADF generic versions of the product from the market in those circumstances and to expeditiously finalize guidance for generic manufacturers on the development of generic ADF products. We urge that the FDA use its existing authorities to expedite the review of and encourage the development of non-opioid pain medications, ADF products, products to treat opioid addiction, and products that can prevent opioid drug overdose and death, including generic products. Further, we need to ensure policies regarding coverage and access of these medicines is appropriate a given the public health benefits of such products.

- *Clarify regulations to support law enforcement efforts to shut down key sources of diversion, including rogue online pharmacies and "pill mills," and prosecute the perpetrators.* Clarifying the regulations related to legitimate pain management clinics would facilitate law enforcement's ability to shut down and prosecute those operating "pill mills." For example, "pill mills" pose as legitimate pain management clinics but inappropriately provide controlled substances often on a cash-only basis and without requiring a prescription solely for financial gain. The National Association of Board of Pharmacy has reported that "despite the perception that illegal purchases of prescription opioids only take place with drug dealers on the street, rogue internet drug outlets serve as dealers hiding behind sleek websites that look safe to people trying to purchase CS [controlled substance] medications.[iv]

- *Expand treatment capacity, coverage, and access.* The National Institute on Drug Abuse (NIDA) defines "addiction as a chronic, relapsing brain disease that is characterized by compulsive drug seeking and use, despite harmful consequences. It is considered a brain disease because drugs change the brain; they change its structure and how it works."[v] While this reinforces the challenges associated with treating this disease, addiction is a treatable, chronic disease that can be managed successfully. As documented by the peer-reviewed research, behavioral therapy combined with medication-assisted treatment can help ensure success for most patients. However, treatment approaches must be individualized to address each patient's particular circumstances and any other medical, psychiatric, and social problems. Importantly while many patients relapse that does not mean treatment failed, rather it suggests that the treatment plan needs to be reevaluated. The nature of addiction also underscores the importance of having multiple treatment options that can be tailored to prescriber and patient needs.

We support a comprehensive treatment approach that includes:

- Expanding treatment capacity
- Increasing coverage and access to the full range of treatment and recovery services needed, which range from a range of in-patient and out-patient treatment options, medication-assisted treatment, including opioid reversal agents, and medication-assisted therapies in combination with other treatment options.

Competitive Dynamics for Medication-Assisted Treatments including Opioid Reversal Agents

There are currently a range of medications available to (1) reverse the effects of an opioid overdose and (2) treat addiction, with some of the medications in the latter category also approved to treat alcohol addiction. Demand for these products has increased substantially in a relatively short period of time. Among the drivers of demand is the increased rate of deaths from overdose, which is creating a tremendous burden on families, our health care and law enforcement infrastructure, and communities around the country; efforts to reduce the stigma associated with addiction which is encouraging more people to seek treatment as well as increased awareness and education; and changes in policy at the state and federal levels that have sought to broaden access to therapies.

Before delving into the specifics of these markets, it is important to put into perspective the overall U.S. biopharmaceutical market where substantial competition exists—both brand to brand and brand to generic. A few key facts:

- The competitive market is structured to take maximum advantage of savings from brand competition. Brand medicines face competition well before approval, as companies race to be first to market. Multiple companies simultaneously compete to research, develop, and secure FDA approval of first-in-class treatments. In fact, 88% of first-in-class medicines launched between 2005 and 2011 already had a competitor in Phase II clinical development at the time of their launch. Once launched, the time a medicine is alone in its class is 2.3 years for drugs approved between 2005 and 2011.[vi]

- Following generic entry, the U.S. market continues to drive long-term affordability by taking maximum advantage of the savings provided by generic drugs.
  - Today, more than 90% of all medicines prescribed in the U.S. are generics—due largely to the concentration of purchasing power by payers and the aggressive use of utilization management tools to rapidly shift utilization towards generics.
  - Continued competitive pressure resulting from the loss of intellectual property (IP) protection and the entry of more generics and biosimilars is expected to continue to fuel this dynamic in the years ahead. Between now and 2020, an estimated $93 billion of U.S. brand sales are projected to face generic competition.

- For brand medicines facing generic entry in 2013-2014, generics captured an average of 93% of the market (by volume) within a year of entry, compared to 56% in 1999-2000.[vii][viii] In other words, brand medicines retained an average of only 7% of market share at one year post-generic entry in 2013-2014, compared to brand medicines maintaining a market share of 44% in 1999-2000.

In both the market for overdose reversal agents and medicines to treat addiction, generics have been available for decades and comprise the majority of medicines prescribed today. In addition, there are several brand or innovative drugs currently available in these therapeutic areas that constitute significant medical advances for addressing opioid abuse and addiction .

In recent years, there has been an increasing public health need for ADF versions of pain medicines, non-opioid analgesics, as well as new therapies to help treat addiction and to reverse opioid overdose. This increased demand is being driven by a number of factors, including changes to policies at the federal and state levels to address the rising epidemic related to addiction and overdose, such as the recently passed Comprehensive Addiction and Recovery Act of 2016, which included a range of provisions aimed at expanding access among first responders to opioid reversal agents as well as efforts to expand access to medication-assisted treatments for addiction. In addition, there are many new innovative medicines in development to address this growing demand. According to a September 2016 search of the Adis R&D Insight Database, there were an estimated 31 ADF products for the treatment of pain, 35 addiction medicines, and close to 40 non-opioid pain medicines in clinical development. While only 12% of drugs in development reaching clinical trials are ultimately approved by the FDA,[ix] the pipeline speaks to the potential for additional new options for patients in the coming years and the potential for increased competition in this space.

As companies assess whether to invest in R&D in a particular area they consider the potential market and whether there will be demand for their medicine. Federal and state policies have increasingly been focused on seeking to expand access, which creates an incentive for the development of new therapies, which in turn drives brand to brand competition and ultimately generic competition as well. Companies must ultimately assess an array of factors in determining whether or not to enter a market, including whether they can develop a medicine that is an improvement over existing treatments (e.g., whether the product can result in better health outcomes, improve patient adherence and quality of life, reduce side effects, or provide more convenient dosing and delivery methods), whether they can make the case to payers of the value of the treatment.

A brief overview of the current marketplace for some of the existing therapies for opioid reversal and addiction treatment are detailed below.

Medication-Assisted Treatments for Overdose Reversal

Opioids in high doses can lead to respiratory depression and death. The effects of opioid overdose can be reversed if the person receives basic life support and the timely administration of the medication naloxone. Naloxone products sometimes referred to as "rescue drugs" or "overdose reversal agents" are used to counter the effects of overdose from heroin and other opioids. These medications are not controlled substances, meaning they have no potential for abuse. They only have an effect in a person that has opioids in his/her system.

Naloxone currently is purchased by a number of different stakeholder groups with differing needs and preferences, including acute care settings such as hospitals and clinics, jails, first responders, community-based groups, and caregivers. Each stakeholder group differs in terms of preferred method of delivery for the medicine, with acute care settings more likely to prefer to administer the medicine via syringe whereas caregivers and many first responders prefer the use of other delivery mechanisms such as via auto-injector or nasal spray.

The marketplace for naloxone products is unique compared to many other therapeutic areas. At the state level, access to naloxone products historically has been limited to circumstances in which there was a direct physician-patient relationship and providing the drug to anyone other than the patient was prohibited by law. In recent years, however, many states have sought to update their laws to expand access to naloxone among those likely to be in a position as first responder such as paramedics and other emergency medical services personnel, law enforcement, pharmacists, and parents and other caregivers. Many states' regulations allow pharmacies to dispense naloxone without a patient being present with a prescription through standing order or collaborative practice agreements with prescribers.

This has resulted in a bifurcated system in which many states permit the purchase of naloxone outside of the normal drug distribution system and often without a prescription. CVS,[x] for example, announced in 2015 that naloxone will be available without a prescription in 14 states, and in 2016, Walgreens announced the roll out of a program across 35 states to make naloxone available without a prescription by the end of the year.

Other key aspects of the naloxone market:

- Naloxone is produced and sold by 8 different biopharmaceutical manufacturers. There are 6 generic manufacturers in a range of dosage forms and there are also 2 brand naloxone medications offering convenient delivery systems (see below). Relative to the market in early 2015, the number of manufacturers in this space has close to doubled.

- The branded products include:

  - Narcan, approved in 2015, is the first nasal form of the drug that enables users to administer the medication without the use of a syringe. In the approval letter for this

medicine, the FDA noted that many first responders and caregivers felt that a nasal spray formulation of naloxone was easier to deliver, and avoided the risk of contaminated needles. As a result, prior to the approval of Narcan, there had been widespread use of unapproved naloxone kits using an injectable formulation of naloxone along with an atomizer to deliver the medicine off-label nasally. Today, according to FDA, "people have access to an FDA-approved product for which the drug and its delivery device have met the FDA's high standards for safety, efficacy and quality."[xi] Also of note, in late 2015, the FDA denied approval of another nasal form of the medication.

- Evzio, approved in 2014, is the first drug-device combination product that delivers a single dose of naloxone via a hand-held auto-injector. Once turned on, the device provides verbal instruction to the user describing how to deliver the medication.[xii]

- Since 2011, naloxone sales have increased from 4.4 million units to 6.1 million units:

  - In the past 2 years, there has a 40% increase in volume.
  - While there's been growth across all channels, the vast majority has been in retail pharmacy—where growing demand for more convenient delivery mechanisms has resulted in the entry of new branded products—particularly among first responders and non-healthcare professionals.

As demand increases along with heightened interest in alternative forms of delivery to meet various user needs, it is likely that competition will increase in this space.

Medication Assisted Treatments for Addiction

Medications to treat addiction include the following:

- **Buprenorphine and buprenorphine-naloxone—**These medicines seek to suppress withdrawal symptoms and cravings—it is primarily used for the withdrawal phase of opioid dependence. The combination products compete with other opioids by suppressing withdrawal symptoms and cravings and are combined with naloxone to diminish the potential for misuse.
- **Naltrexone—**These medicines block opioid receptors involved in opioid's euphoric effects.
- **Methadone--**These medicines compete with other opioids by suppressing withdrawal symptoms and cravings.

Key aspects of the market include the following:

- Buprenorphine and buprenorphine-naloxone products comprise more than 70% of medication-assisted treatments by volume and sales (based on unpublished analysis from IMS Health).

- Since 2011, sales of buprenorphine and buprenorphine-naloxone combination products have grown from 226 million extended units to 368 million extended units, with unit referring to a standardization of the various forms of the products—indicating a relatively steady growth in demand of about 63% over the past 5 years.

- Generics have become a growing share of the market as demand has grown:
  - Since 2011, sales of generic buprenorphine products have grown from 30 million units to 148 million units.
  - Today generic products represent more than 40% of the buprenorphine market whereas, 5 years ago they represented just 13%.

- There are currently 19 manufacturers of buprenorphine and buprenorphine-naloxone combination products currently on the market to treat addiction, including 4 manufacturers of brand medications:
  - Bunavail, approved in 2014, is the first and only formulation of buprenorphine and naloxone for buccal (inside of the cheek) administration providing an important delivery alternative.
  - Zubsolv, approved in 2013, is a once-daily, sublingual tablet formulation that fully dissolves within minutes.
  - Suboxone, approved in 2002, is intended to be used in maintenance treatment of opiate addiction and is available in a tablet form that is placed under tongue and must be allowed to dissolve.[xiii]
  - The first buprenorphine implant, Probuphine, for the maintenance treatment of opioid dependence was approved in May 2016. Probuphine is designed to provide a constant, low-level dose of buprenorphine for 6 months in patients who are already stable and on low-to-moderate doses of other forms of buprenorphine, as part of a complete treatment program. The FDA approval letter noted that this medicine "provides a new treatment option for people in recovery who may value the unique benefits of a six-month implant compared to other forms of buprenorphine, such as the possibility of improved patient convenience from not needing to take medication on a daily basis." [xiv]

- There are currently 11 manufacturers of naltrexone products on the market, but there is only one extended-release product, Vivitrol, an innovative product, that is approved to treat and prevent relapse after patients with opioid dependence have undergone detoxification

treatment. This extended-release formulation of naltrexone administered by intramuscular injection once a month. In announcing approval of this new medicine, the FDA stated that "This drug approval represents a significant advancement in addiction treatment."[xv]

- All available methadone products are generic and the overall market share in the addiction space for these medicines has remained stable at between 3 and 4% since 2011.

This very high level review of the marketplace for medications to treat addiction demonstrates there are a large number of generic entrants as well as growth in the entry of new branded therapies that are providing valuable new delivery mechanisms expanding treatment options for prescribers and patients. As mentioned previously, based on the evolving market dynamics and review of the pipeline, competition is expected to further expand and evolve in response to the needs of various purchasers.

More research is needed to determine the impact that insurer tools, such as formulary placement, prior authorization, quantity limits, step therapy, and other tools influence utilization and market incentives. Benefit design should be carefully considered as it can pose barriers to access. Further, it can create disincentives for companies to engage in research to bring new therapies to market if there is not a willingness to cover and reimburse for innovative new treatments.

Conclusion

PhRMA applauds your continued commitment to addressing opioid abuse. Just as overdose prevention and addiction treatment and the recovery process are multi-faceted, so too is the overall challenge of preventing diversion and abuse of prescription medicines. We look forward to continuing to work with the Subcommittee, members of Congress, and other stakeholders on these important issues.

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[i] http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6450a3.htm

[ii] Curtis, F, et al. The Economic Burden of Prescription Opioid Overdose, Abuse, and Dependence in the United States, 2013, Medical Care 2016(54)10: 901-6.

[iii] Among the most abused prescription medicines (opioids, CNS drugs, and stimulants) an estimated 93.6% of prescriptions at the retail level were for generic medicines in calendar year 2013. PhRMA analysis IMS National Prescription Audit, June 2014.

[iv] National Association of Boards of Pharmacy. *Internet Drug Outlet Identification Program Progress Report for State and Federal Regulators: July 2016* cited in http://www.news-medical.net/news/20160730/NABP-report-points-rogue-internet-drug-outlets-serve-as-dealers-to-people-purchasing-controlled-substances.aspx

[v] https://www.drugabuse.gov/publications/media-guide/science-drug-abuse-addiction-basics

[vi] Tufts Center for the Study of Drug Development. First in class drugs in competitive development races with later entrants. Tufts CSDD Impact Report. 2015(17):6.

[vii] Grabowski, G, et al. "Updated Trends in US Brand-Name and Generic Competition," Journal of Medical Economics, April 11, 2016, http://www.tandfonline.com/doi/abs/10.1080/13696998.2016.1176578.

[viii] Generic erosion for all NMEs was 88% as brand medicines retained an average of 12% of market share (by volume) at 1 year post-generic entry 2013-2014.

[ix] Tufts Center for the Study of Drug Development. Briefing: Cost of Developing a New Drug, November 18, 2014. Tufts Center for the Study of Drug Development & Tufts School of Medicine.

[x] In 2015, CVS announced that it would sell Naloxone without a prescription in Arkansas, California, Minnesota, Mississippi, Montana, New Jersey, North Dakota, Pennsylvania, South Carolina, Tennessee, Utah and Wisconsin. The company already sold naloxone without a prescription in Massachusetts and Rhode Island. States where naloxone will be available through Walgreens without a prescription at its pharmacies: Alabama, Arkansas, California, Colorado, Connecticut, District of Columbia, Idaho, Illinois, Indiana, Kentucky, Louisiana, Maine, Maryland, Massachusetts, Minnesota, Mississippi, Montana, Nebraska, New Hampshire, New Jersey, New Mexico, New York, North Carolina, Ohio, Oklahoma, Oregon, Pennsylvania, Rhode Island, South Dakota, Tennessee, Texas, Utah, Vermont, Virginia, Washington, and Wisconsin.

[xi] http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm473505.htm

[xii] http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm391465.htm

[xiii] http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm191521.htm

[xiv] http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm503719.htm

[xv] http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm229109.htm