

OCTOBER 2018

Orphan Drugs in the United States

Growth Trends in Rare Disease Treatments



Introduction

Rare diseases have increasingly been discussed in the media over the past several years as the number of new treatments has surged and provided new health benefits to patients. There are approximately 7,000 rare diseases that affect 25 to 30 million people in the United States - more than half of whom are children - but treatments are available for just 5% of them. Many of these diseases are life-threatening or life-limiting, and while some conditions can now be treated and managed as chronic conditions, for the first time new curative treatments are bringing the prospect of a better life to some patients. Even with a dramatic increase in the numbers of orphan drugs approved in the past few years, challenges persist for the rare disease community, including a need for increased awareness from medical professionals and elected officials, as well as for funding for research to develop treatments and cures.

This report, which updates an analysis of the orphan drug market published by the QuintilesIMS Institute in 2017, provides a historical perspective on the characteristics of rare diseases, their treatments and the role of the Orphan Drug Act of 1983 in advancing rare disease medicines. It describes the characteristics of orphan drug spending, volumes and prices, placing orphan drugs in the context of specialty drug trends and overall medicine spending levels and growth.

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The contributions of Onil Ghotkar, Deanna Nass, Urvashi Purval, Vismaye Raje, Alana Simorellis, Durgesh Soni and others at IQVIA are gratefully acknowledged.

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Executive summary

There are approximately 7,000 rare diseases affecting 25–30 million Americans. A large number of rare diseases remain without effective treatments despite over 500 orphan drug therapies having been approved in the United States. However, a growing focus by researchers and the FDA on rare disease therapies have resulted in a dramatic increase in the number of new therapeutic options for these patients in the past two years. The creation of the orphan drug designation with the passage of the Orphan Drug Act in 1983 has facilitated the development and approval of drugs for rare diseases, and years 2017 and 2018 were marked by the highest number of orphan drug and indication approvals to date. The FDA approved 80 new orphan indications in 2017 and 57 just within the first eight months of 2018, the highest numbers annually since the passage of the Orphan Drug Act.

The combination of scientific advances – such as those made in genetics, the application of next-generation therapeutic approaches such as gene therapy and the use of biomarkers to identify diseases – along with accelerated product review and a growing commitment by policy makers to advance precision medicine, is fueling the increased number of orphan therapies.

Orphan drugs can be expensive for patients and payers alike. However, there is generally an inverse relationship between the price of these therapies and their volume of use, given that orphan drugs are developed for small patient populations. Although the median annual cost for an orphan drug in 2017 was over \$46,800, the median annual cost for the top ten rare disease therapies used by the greatest number of patients was much lower at \$1,216. Overall, drug spending in the United States is evolving from an emphasis on high-volume, low-cost drugs for chronic diseases toward drugs with lower volumes but with higher value in terms of patient outcomes. Other dynamics affecting

drug spending in the United States in 2018 include the greater proliferation of specialty formulary tiers, greater use of health plans involving pharmacy deductibles and patient co-pays, expanded use of specialty pharmacies and limited distribution networks, and strengthened negotiating power of pharmacy benefit managers, the net result of which is significant financial burden for patients overall.

Of the 503 orphan drugs approved as of August 2018, 394 (78%) had only orphan indications and 109 (22%) had both orphan and non-orphan indications. Of the 109, 60 received approval for a non-orphan indication first and 13 received approval for both orphan and non-orphan indications simultaneously.

The orphan drug share of the total volume of pharmaceuticals used in the United States declined from a peak of 0.6% in 2003 to 0.3% in 2015 but has risen to 0.4% by 2017. Total drug spending in the United States in 2017 was \$451 billion, with 55.7% spent on non-orphan traditional drugs, 34.7% spent on non-orphan specialty drugs and 9.6% spent on orphan indications of approved orphan drugs. Spending on orphan indications has increased moderately as a share of spending and these drugs represent only a small part of the overall medicine budget.

Definitions

It is helpful to use a set of common definitions to fully understand the role that orphan drugs play in the U.S. health system, both from a volume and cost perspective. For the purposes of this report, the following terms are used:

- **All medicines** include those prescription drugs approved by the FDA and distributed through retail and non-retail channels, including brands and generics, specialty and traditional drugs, and small molecules as well as biologics
 - **Specialty medicines** as defined by IQVIA are those medicines that treat chronic, complex or rare diseases and have a minimum of four out of seven of the following additional characteristics:
 1. List price is in excess of \$6,000 per year
 2. Initiated/maintained by a specialist physician
 3. Requiring administration by another individual or healthcare professional (i.e., not self-administered)
 4. Requiring special handling in the supply chain (e.g., refrigerated, frozen, chemo precautions, biohazard)
 5. Requiring patient payment assistance
 6. Distributed through non-traditional channels (e.g., "specialty pharmacy")
 7. Medication has significant side effects that require additional monitoring/counseling (including, but not limited to, REMS programs) and/or disease requires additional monitoring or therapy (e.g., monitoring of blood/cell counts to assess effectiveness/side effects of therapy).
- The definition of specialty drugs often differ among stakeholders. For example, Centers for Medicare & Medicaid Services (CMS) defines specialty drugs only in the context of Part D (i.e., not Part B) and uses a dollar threshold; pharmacy benefit managers typically define specialty also based on cost; and pharmaceutical wholesalers consider specialty drugs to be those that require special handling due to low volume, cold-chain or other storage requirements, or are managed through separate organizational or delivery channels.
- **Traditional medicines** are defined by IQVIA as all drugs that do not meet the criteria to be classified as a specialty medicine.
 - **Orphan drugs** are generally defined as those medicines with one or more indications approved under the Orphan Drug Act. In some cases, these medicines may also have additional non-orphan indications approved by the FDA but that do not meet the criteria for an orphan drug designation.
 - **Drug spending** in this report measures the total value of spending on medicines in the United States by pharmacies, clinics, hospitals and other healthcare providers and includes generics, branded products, biologics and small-molecules in retail and non-retail channels. It is based on IQVIA reported values from wholesaler transactions measured at trade/invoice prices and exclude off-invoice discounts and rebates that reduce net revenue received by manufacturers.
 - **Drug volumes** are measured in this report in extended units, which are the smallest dose unit of a medicine such as pills and vials, across all types of drugs. This is a rough measure of volume which has a limitation that dissimilar items are not normalized to an equivalent volume, but they serve as a general indicator of how widely medicines are used.

Characteristics of rare diseases and their unique challenges

- Rare disease patients and their families, caregivers and healthcare providers face unique challenges.
- Rare conditions are often poorly diagnosed and less well-understood.
- Patients often face delays in diagnosis for rare diseases of several years and visit an average of 7.3 physicians before receiving a diagnosis.
- Patients bear a large burden from the effects of their disease as well as direct and indirect monetary costs.

There are approximately 7,000 rare diseases that affect 25 to 30 million people in the United States – more than half of whom are children.^{1,2} Rare disease patients and their families, caregivers and healthcare providers face unique challenges. Because their clinical needs differ from those of patients with more common conditions and their conditions are often poorly diagnosed and less well-understood, these patients bear a large burden from the effects of their disease as well as direct and indirect monetary costs. Rare disease patients may require many expensive medical tests and frequent visits to multiple specialists, leading them to face significant direct monetary costs. Disruptions in day-to-day life for the patients and their families additionally can lead to large indirect costs, such as lost work days.

These patients often struggle to receive diagnosis and support despite a growing awareness of rare diseases among healthcare stakeholders. Patients often face delays in diagnosis for rare diseases of several years and visit an average of 7.3 physicians before receiving a diagnosis.³ In addition, the number of rare disease specialists is limited, and it can be difficult to find a specialist, which contributes to the challenges around receiving an accurate and timely diagnosis.⁴

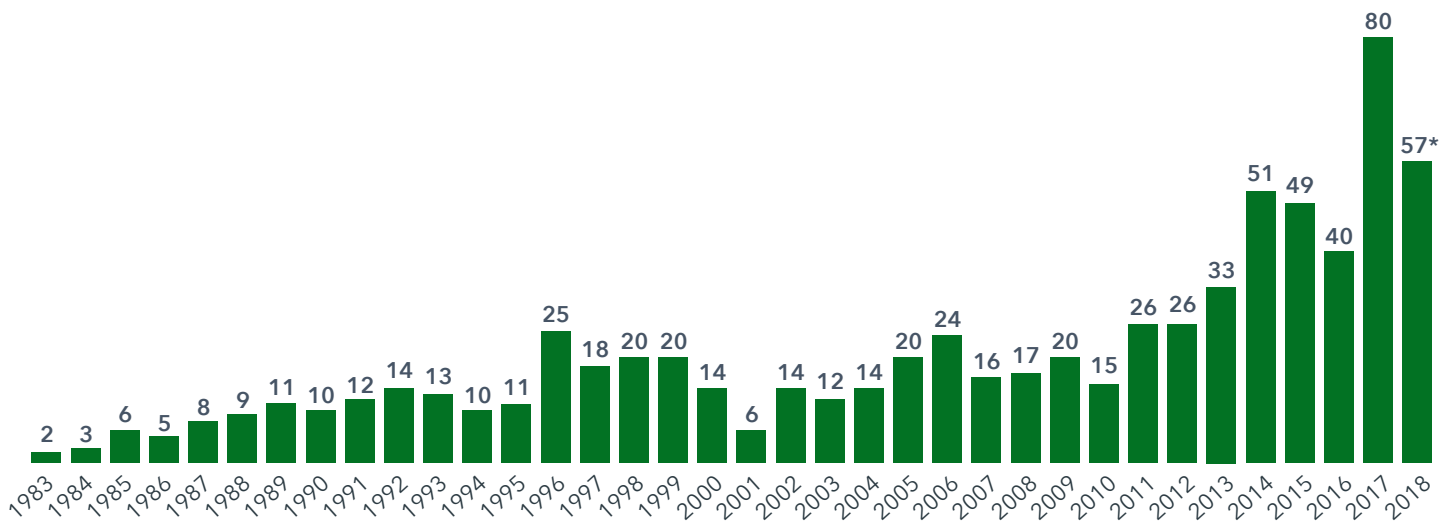
The Orphan Drug Act of 1983

- The Orphan Drug Act continues to support the development of innovative treatments for rare disease patients.
- Over the past two years, the FDA approved the greatest number of both orphan indications and new orphan drugs since the passage of the Orphan Drug Act in 1983.
- By August 2018, there were 503 approved orphan therapies with 731 designated and approved orphan indications.
- In 2017, the first action to reduce incentives in this area was taken when an update to the Orphan Drug Act reduced the Orphan Drug Tax Credit from 50% of applicable clinical costs to 25%.

The past two years have brought both the greatest number of new orphan drug designations awarded and the greatest number of orphan indication approvals since the passage of the Orphan Drug Act in 1983, notably demonstrating the success of this legislation. In just 2017 alone, the FDA granted orphan designations to over 429 unique drugs under development.⁵ The FDA additionally approved 80 new orphan indications

in 2017 and 57 just within the first eight months of 2018 (see Exhibit 1).⁵ Drug manufacturers continue to increase their focus on the development of therapies for orphan indications and half of the 42 new active substances (molecules not previously approved as a medicinal product) launched in the United States in 2017 were orphan drugs.⁶

Exhibit 1: Number of Orphan Indications Approved in the United States 1983-2018



Source: FDA. Search Orphan Drug Designations and Approvals. 2018 Sep. Available from: <https://www.accessdata.fda.gov/scripts/opdlisting/opod/>
 Note: * Reflects drug approvals through Aug 2018. Exhibit displays designated and marketing approved indications by marketing approval date.

THE ORPHAN DRUG ACT OF 1983

Exhibit 2: Key Elements of the Orphan Drug Act

ORPHAN DRUG ACT ELEMENT	DESCRIPTION	IMPACT
Rare disease definition	<ul style="list-style-type: none"> < 200,000 patients in the United States or > 200,000 patients but with no reasonable expectation that the cost of development will be recovered* 	The intent of the Orphan Drug act is to incentivize drug manufacturers to provide treatments for rare diseases.
Market exclusivity	<ul style="list-style-type: none"> Seven-year market exclusivity for sponsors of approved orphan drugs or products 	The market exclusivity for a new chemical entity in the United States is typically five years after FDA approval, however for orphan drugs the FDA will not award market authorization for a generic drug for the rare disease for seven years post-approval. This incentive is superior to traditional IP patent protection and a substantial incentive.
Tax incentives	<ul style="list-style-type: none"> The Orphan Drug Tax Credit (ODTC) allows orphan drug developers to collect tax credits for expenses incurred for U.S. clinical trials on the orphan indication 	The ODTC lowers the cost of drug development. A study from NORD estimates that 33% fewer orphan drugs would be developed without the ODTC.*** At the end of 2017, the ODTC was reduced from 50% to 25% of qualified clinical testing expenses.
Clinical research subsidies	<ul style="list-style-type: none"> The Orphan Product Grant program provides funding for clinical testing of new therapies to treat and/or diagnose rare diseases** 	<p>The grant program lowers the cost of drug development. According to the FDA, the Office of Orphan Products Development (OOPD) has received over 2,500 applications, reviewed over 2,300, funded over 700 studies and helped more than 60 products gain marketing approval.</p> <p>Receiving a grant from the Orphan Product Grant program increases the likelihood of marketing authorization.</p>
Other regulatory incentives	<ul style="list-style-type: none"> Orphan drugs and products are exempt from the usual new drug application or "user" fees charged by FDA (i.e., PDUFA) 	These regulatory incentives lower the cost of drug development and enable therapies to reach patients sooner.

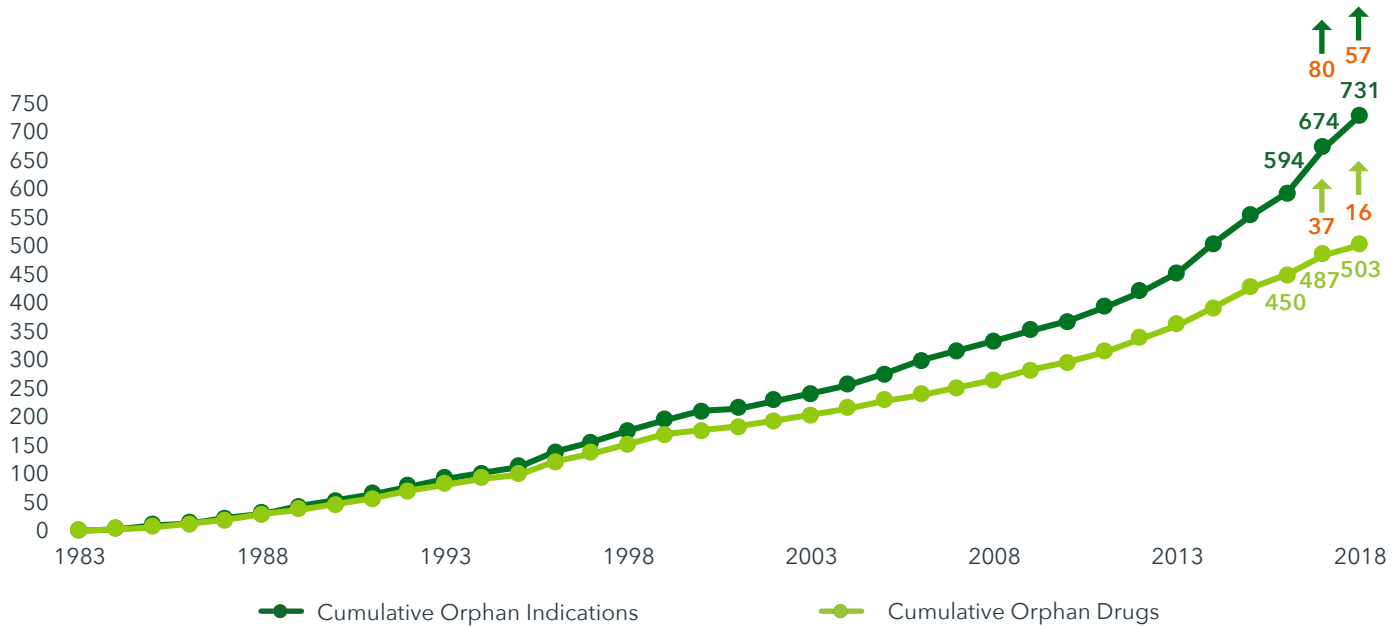
Sources FDA.gov; Cheung R, Kohler J, Illingworth P. Health Law Journal. 2004; NORD Impact of the Orphan Drug Tax Credit on treatments for rare diseases 2015; oig.hhs.gov. For full references see: 9,11,12,13,14,15

Notes: *Only three therapies have received orphan drug designation under this second definition for rare diseases.⁷ **Grants are modest and can run approximately \$500,000/year. ***Study based on an ODTC of 50% from that period and not the current 25%.

These statistics stand in sharp contrast to the few rare disease approvals seen in the two decades preceding the passage of the Act. At that time an estimated 34 drugs were approved for rare diseases (based on the current definition) from 1967 to 1983, and as few as ten were approved in the decade prior to 1983.^{7,8}

Rare disease patient advocacy groups successfully lobbied for the passage of the Orphan Drug Act (1983), and amendments were made subsequently in 1984, 1985 and 1988 (see Exhibit 2). The act has been universally considered a success, however, the latest update to the Act occurred in 2017 and reduced the

Exhibit 3: Number of Orphan Indications and Orphan Drugs 1983-2018



Source: FDA Orphan Drug Database; Drugs@FDA Database, FDA websites; IQVIA Institute, Sep 2018

Note: The graphic was created using a curated list of orphan indications and approvals based on the FDA Orphan Drug Database. Includes drug approvals through Aug 2018.

Orphan Drug Tax Credit from 50% of applicable clinical costs to 25%.⁹ This was the first action to effectively reduce incentives in this area since the passage of the original law, and the action was tied to concerns around orphan approvals for drugs already on the market and a push for tax savings.¹⁰

From 1983–June 2018, there have been a total of 7,394 orphan drug designation requests, with the number of requests ranging over time from 16 in 1983 up to 715 in 2017.^{16,17,18} Separately, in 2017 there were 80 new orphan

indications approved and 57 in 2018 through August (see Exhibit 3). Many of these indications were awarded to already marketed orphan drugs. Overall, 37 unique drugs obtained their first approval of an orphan indication in 2017 and of these 21 were new active substances (NAS) - with 10 in oncology – while another 16 unique drugs obtained their first orphan approvals through August 2018 (see Exhibit 3).^{6,19} In total there were 503 unique approved orphan drugs that have received approval for 731 orphan indications since 1983.

* Number includes 5,792 orphan drug designation requests reported 1983-2015 and 1,602 requests 2016–June 2018 combining sources

Orphan drug therapies

- Drugs launched in 2017 include ground-breaking treatments for patients with lysosomal storage disorders, therapies for neuromuscular diseases, such as spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS), the first non-blood product for hemophilia A, an antisense oligonucleotide product and an effective gene therapy.
- Cost can be a challenge for rare disease patients and their families with the median annual invoice price for a single therapy amounting to over \$46,000 in 2017.
- The top ten therapies used by the greatest number of patients averaged \$9,676 per year in 2017.
- There is an inverse relationship that exists between the cost per year for a therapy and the number of patients, with less expensive therapies typically for larger patient populations.
- In 2017, rare diseases oncology medicines made up the bulk of orphan products, and these therapies ranged from approximately \$1,000 to just under \$500,000 per year.

Orphan drugs and biologics approved in 2017 and 2018 address a wide range of diseases, many of which are used to treat pediatric and rare inherited diseases. Of note, 2017 saw the launch of two ground-breaking treatments for patients with lysosomal storage disorders that previously had no available treatments. A number of newly available therapies were for the treatment of neuromuscular diseases, such as spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS) (see Exhibit 4). In addition, there was a significant advance for the treatment of hemophilia A with the availability of the first non-blood product, and an effective gene therapy became available, with the expectation of more gene therapies launching in the years to come.

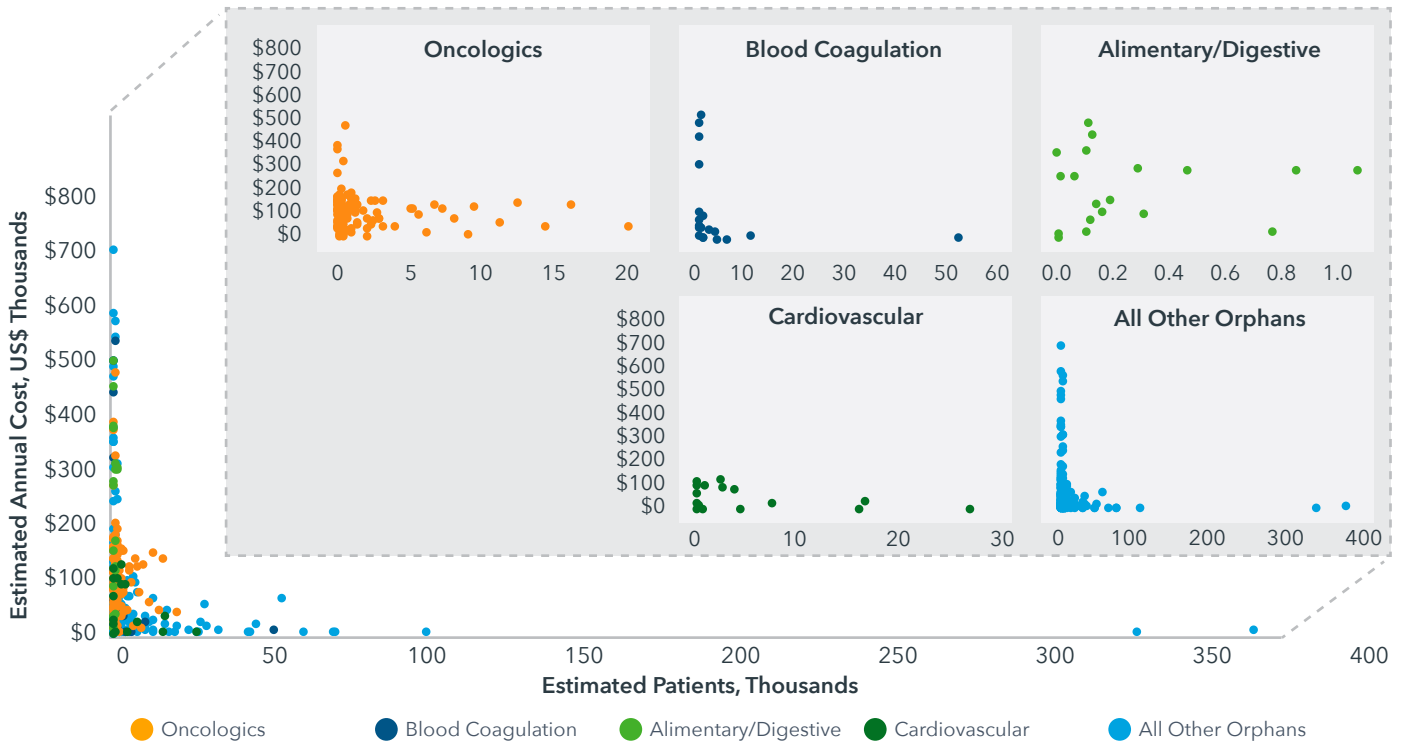
Analysis conducted for the report found that orphan drugs that are used to treat small populations are often more expensive than non-orphan medicines. In this report, the average estimated patient population per orphan therapy was 5,730, although the median was 519. The median annual cost (at invoice prices) for an orphan drug in 2017 was over \$46,800 per year (mean average is \$87,319). However, a number of orphan therapies have a more modest cost. An inverse relationship exists between the cost per year for a therapy and the number of patients, with more expensive therapies being dispensed to relatively few patients (see Exhibit 5). In contrast, the ten orphan therapies used by the greatest number of patients averaged \$9,676 per year (the median cost was \$1,216) and include therapies such as Suboxone for treatment of addiction, Copaxone for the treatment of multiple sclerosis, and the anti-infective Alinia.

Exhibit 4: Characteristics of Selected Rare Disease Medicines Launched in 2017

CHARACTERISTICS	MEDICINE EXAMPLE
An innovative therapy for a pediatric population with a lysosomal storage disorder affecting the nervous system	Cerliponase alfa (Brineura) was approved in April 2017 to slow loss of walking ability in symptomatic, pediatric patients with late infantile neuronal ceroid lipofuscinosis type 2 (CLN2). ²⁰ CLN2 is caused by changes in the TPP1 gene and is one of the common forms of neuronal ceroid lipofuscinosis (NCL), a group of inherited lysosomal storage disorders often referred to as Batten disease. Deficiencies in the TPP1 enzyme can cause neurological and vision problems and shortened life expectancy. Cerliponase alfa is the first and only therapy approved for patients with CLN2 and is expected to improve quality of life for CLN2 families. It is also the first enzyme replacement delivered via intraventricular infusion into a ventricle in the brain.
An innovative antisense oligonucleotide therapy for a neuromuscular disease	Nusinersen (Spinraza) was approved by the FDA in December 2016 for the treatment of children and adults with spinal muscular atrophy (SMA). ²¹ SMA is a group of inherited disorders characterized by a loss of motor neurons in the spinal cord due to a mutation in the survival motor neuron 1 (SMN1) gene. SMN1 codes for the SMN protein, and without a proper level of SMN, there is progressive muscle weakness and atrophy. Nusinersen is a survival motor neuron 2 (SMN2)-directed antisense oligonucleotide, which modulates an alternate splicing of the SMN2 mRNA transcript and leads to an increase in production of a functional SMN protein in motor neurons. Nusinersen is one of the first effective therapies available to SMA patients and is one of few available antisense oligonucleotide therapies in the United States.
First gene therapy for an ophthalmic disease	Voretigene neparvovec (Luxturna) was approved by the FDA in 2017 for the treatment of adult and pediatric patients with confirmed, biallelic RPE65 mutation-associated retinal dystrophy; a rare, hereditary retinal dystrophy that leads to progressive vision dysfunction and sometimes blindness. Voretigene neparvovec is a viral-vector based gene therapy that delivers the fully functioning RPE65 gene directly to the retinal cells of the eye and replaces a copy of the faulty gene. According to the FDA, voretigene neparvovec "is the first directly administered gene therapy approved in the U.S. that targets a disease caused by mutations in a specific gene." ²² Patients receiving treatment with voretigene neparvovec in the clinical development program were able to better navigate an obstacle course in low light than patients not receiving the therapy and showed improvement a year after treatment. Previously, there was no effective treatment available to these patients and voretigene neparvovec has the potential to improve visual function and activities of daily living in these patients.
First preventive non-blood product for an inherited bleeding disorder	Emicizumab (Hemlibra) was approved to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A who have developed antibodies against clotting Factor VIII. Almost a third of patients with hemophilia A, when treated with replacement factor VIII, can develop antibodies (inhibitors) against the replacement factor, reducing the effectiveness of the therapy. ²³ Emicizumab is a first-in-class, prophylactic therapy that bridges other Factors in the blood to restore blood clotting for hemophilia A patients with Factor VIII inhibitors. ²⁴ In addition, the therapy is available as a weekly, subcutaneous injection rather than an infusion, and combined with fewer bleeding episodes per year, can greatly increase the quality of life of these patients.
First treatment in many years for a well-recognized neuromuscular disease	Edaravone (Radicava) was approved for the treatment of amyotrophic lateral sclerosis (ALS) to slow the decline in physical function. Also known as Lou Gehrig's disease, ALS is a progressive, fatal disease that attacks nerve cells that control voluntary movement and affects approximately 30,000 people in the United States. ²⁵ Edaravone was initially approved to treat ALS in Japan and is the first approved drug for ALS in the United States in 20 years. ²⁶ Public awareness of ALS was greatly increased following the successful #IceBucketChallenge campaign in 2014 promoted by the ALS Association and others; the campaign raised more than \$200 million dollars which was invested in research programs, education initiatives and patient groups, and almost a third of surveyed participants noted that prior to the challenge, they had no awareness of ALS. ^{27,28} Although there is no cure, the availability of edaravone will provide an additional treatment option to slow disease progression and will help with quality of life in these patients.
New formulation of an older steroid medicine now available in the United States for a neuromuscular disease	Deflazacort (Emflaza) was approved by the FDA for the treatment of patients ages five years and older with Duchenne Muscular Dystrophy (DMD) in 2017; deflazacort was available for treatment of DMD prior to 2017 in other countries and marks the first corticosteroid with approval for DMD in the United States. DMD is one of the most common muscular dystrophies and is characterized by mutations in the DMD gene leading to an absence of the protein dystrophin causing progressive muscle weakness and atrophy. Treatment of DMD is typically via corticosteroids, prednisone or deflazacort, which slow progressive muscle weakness and can delay the loss of independent ambulation by two to three years, although some patients with a specific DMD mutation may be eligible for disease-modifying treatment with eteplirsen (Exondys 51). ²⁹ The availability of additional treatment options for DMD will provide quality of life benefits to these patients and their families.
Enzyme replacement therapy to treat enzyme deficiency in a lysosomal storage disease	Vestronidase alfa (Mepsevii) is an enzyme replacement therapy approved for the symptomatic treatments of Mucopolysaccharidosis type VII (MPS VII). MPS VII, also known as Sly syndrome, is a progressive, inherited disorder that affects most tissues in the body and is caused by mutations in the GUSB gene that create a deficiency of the lysosomal enzyme beta-glucuronidase. MPS VII is a very rare condition, with fewer than 100 patients reported in the United States. ³⁰ Prior to the approval of vestronidase alfa in 2017, MPS VII patients had no approved treatments.

ORPHAN DRUG THERAPIES

Exhibit 5: Estimated Target Patient Population Versus Cost for Orphan Drugs in the United States in 2017, US\$ Thousands



Source: IQVIA National Sales Perspectives, Jan 2018; FDA Orphan Drugs Database, accessed Sep 2018; IQVIA Institute, Sep 2018
 Note: Though scales vary, all x-axes of charts within the zoom box display the number of patients in thousands.

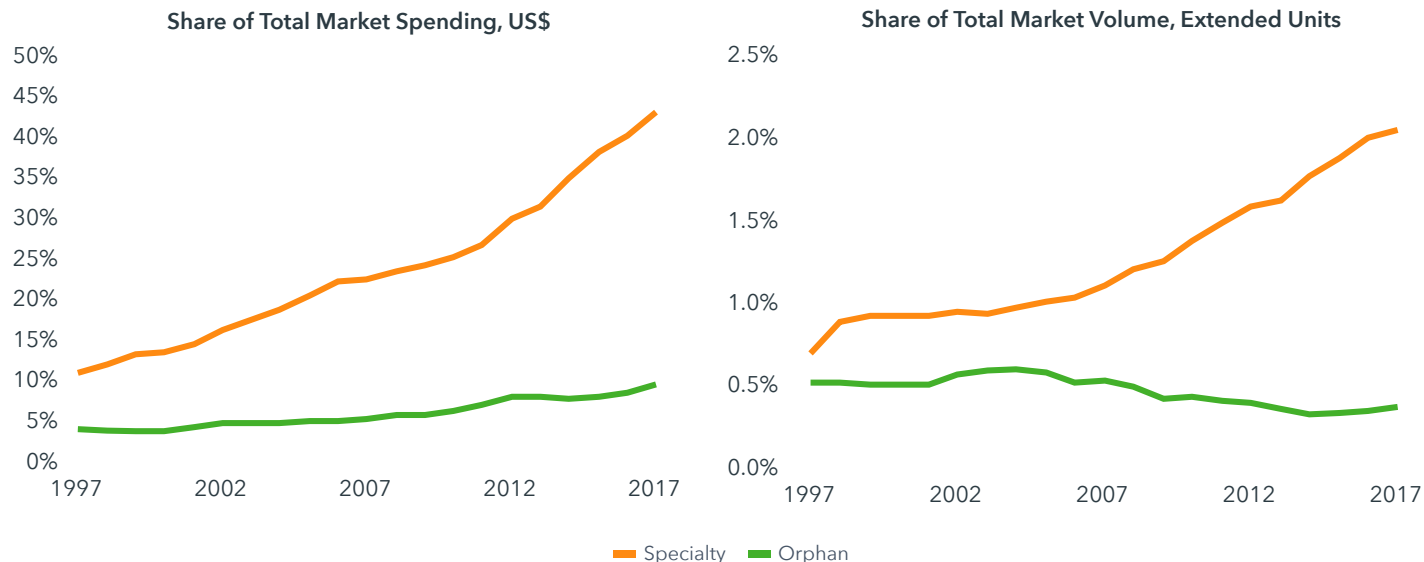
Evolution of U.S. drug spending, use and payer response

- Medicine spending in the United States is shifting from traditional small molecules towards specialty medicines, which treat relatively few people with chronic, complex or rare diseases.
- Many orphan drugs are specialty products and 87% of orphan spending falls within specialty.
- Specialty share of total medicine spending has risen from 11% in 1997 to 43% in 2017, while spending on orphan drugs has risen from 4% to 10% during the same period.
- The evolution of drug spending has been accompanied by cost-saving mechanisms introduced by healthcare stakeholders including: specialty tiers in health plans, patient co-insurance payments, use of specialty pharmacies and limited distribution networks, among others, that increase the cost burden on patients.

In 2017, the total drug spending in the United States (by pharmacies, clinics, hospitals and other healthcare providers) totaled \$451 billion. In the past twenty years, medicine spending in the U.S. market has shifted increasingly towards specialty medicines as perceived opportunities in this area have grown. Rising competition within therapy areas already dominated by traditional medicines and a high-unmet need in the specialty space, facilitated by scientific advances, has attracted investment and contributed to this shift. These specialty medicines typically treat smaller populations of patients with chronic, complex, or rare diseases and encompass a range of complicating factors for drug distribution, administration, and/or payment.

While the majority of orphan drug spending (87%) is made up of specialty drugs, not all orphan drugs are considered specialty medicines; some 37% by drug count are traditional medicines. While specialty share of total medicine spending in the United States has risen from 11% to 43% from 1997 to 2017 (see Exhibit 6), over the same period, spending on orphan drugs has risen more slowly from 4% of overall spending to 10%. This shift has been partly driven by dynamics among traditional medicines, which underwent a significant rise and subsequent fall over the same period as they were used by millions, and then faced patent expiry and became much less costly.

Exhibit 6: Specialty and Orphan Shares of Total Spending and Volume, 1997-2017



Source: IQVIA National Sales Perspectives, Jan 2018; FDA Orphan Drugs Database, accessed Sep 2018; IQVIA Institute, Sep 2018
 Notes: Specialty and orphan shares are based on total market spending or volumes. Specialty and orphan segments overlap, however, some orphan drugs are considered traditional using IQVIA's specialty pharmaceutical definition. Extended units refer to the smallest dose unit of a medicine, typically a pill, vial, or ampoule.

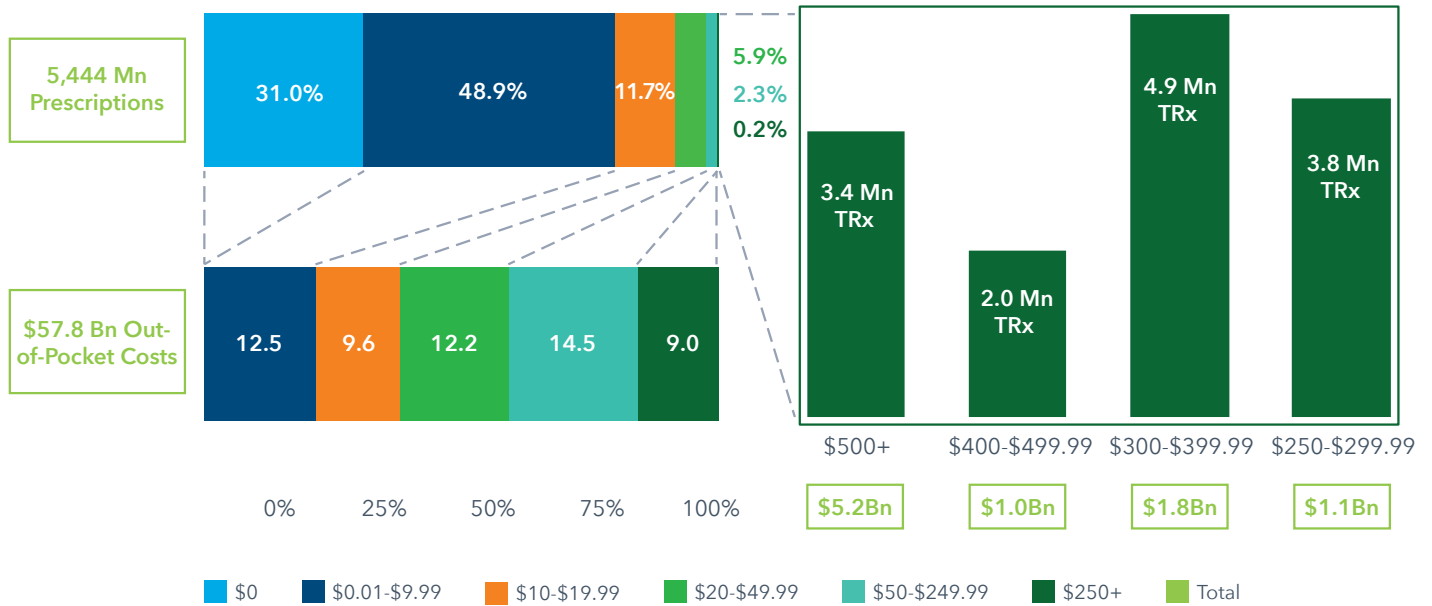
The evolution of drug spending has been accompanied by mechanisms introduced by payers, intermediaries and other stakeholders in their efforts to better manage overall expenditure on medicines and encourage use of the most cost-effective treatments. These approaches and other dynamics that affect drug spending, including that on orphan drugs, and consist of:

- Introduction of specialty tiers in health plans
- Imposition of co-insurance payments by patients, typically as a percentage of a drug's pharmacy cost (see Exhibit 7)⁶
- Greater use of health plans carrying pharmacy deductibles which require patients to pay the full price of their initial prescription costs until they reach their deductible threshold
- The introduction and wider use of (deductible) accumulator insurance plans, which only apply a patient's own out-of-pocket payments toward their deductible, blocking the use of coupons from manufacturers (see Exhibit 8)³¹

- Use of specialty pharmacies and limited distribution networks by manufacturers and payers to exert greater control over pricing and use of drugs
- Increased use of pre-authorization requirements and step therapy guidelines
- Strengthened negotiating power among pharmacy benefit managers, third-party administrators of prescription drug programs, due to consolidation.

A number of orphan drugs are subject to higher out-of-pocket costs, such as shown in the upper cost-tiers of Exhibit 7 (which displays all drugs), where few patients face high costs. Changing benefit designs are also likely to increasingly expose patients with orphan drugs to higher costs.

Exhibit 7: Dispensed Prescriptions and Patient Final Out-of-Pocket Costs by Amount of Cost in the United States in 2017

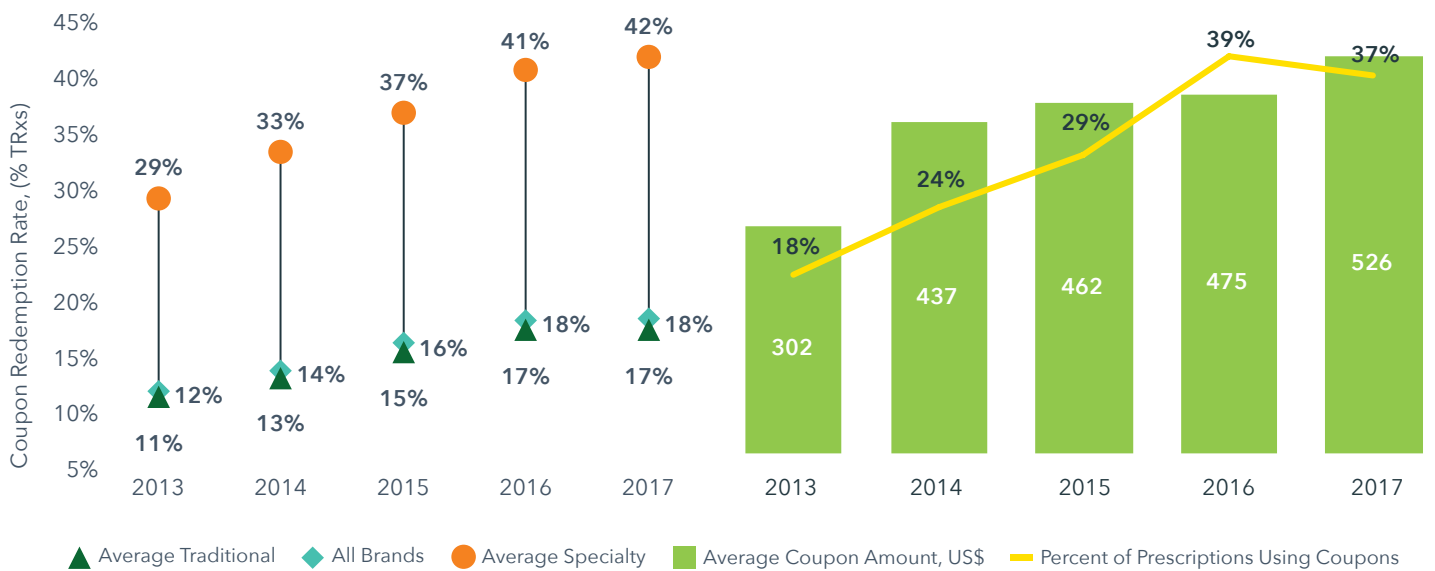


Source: IQVIA Institute for Human Data Science, Medicine Use and Spending in the U.S.: A Review of 2017 and Outlook to 2022, Apr 2018

Patient exposure to cost from high-cost drugs (as orphans often are) can be significant. However, the extensive use of coupons for retail drugs helps offset some patient out-of-pocket costs for these drugs, as

shown with oral cancer therapies in Exhibit 8 (including non-orphan oral products), where nearly 40% of prescriptions use coupons to offset an average \$526 a month.³¹

Exhibit 8: Coupon Redemption Rate for Branded Products and Average Coupon Cost Offset for Oral Oncology Drugs



Source: Left: IQVIA Institute for Human Data Science, Medicine Use and Spending in the U.S.: A Review of 2017 and Outlook to 2022, Apr 2018

Right: IQVIA Institute for Human Data Science, Global Oncology Trends 2018: Innovation, Expansion and Disruption, May 2018

Orphan drugs in context

- Only 9.6% of all drug spending in the United States is attributed to orphan indications.
- Of the \$99.5 billion increase in specialty spending over the last five years, specialty orphan drugs contributed about \$17.5 billion of growth and non-orphan specialty drugs contributed the remaining \$82.1 billion.
- Specialty orphan drugs contributed less than 18% of growth from 2012–2017 with the bulk of growth deriving from medicines with annual costs in excess of \$6,000.
- In 2017, less than 1% of total volume of drugs was the result of orphan therapies being used according to their orphan indications.
- Since 1983, 78% of orphan drug approvals have included orphan-only indications, and the remaining 22% have approvals for both orphan and non-orphan indications.
- Despite an increase in the number of orphan drugs available on the market, the total volume of orphan drugs has declined over the last ten years, though the last three years have shown growth.

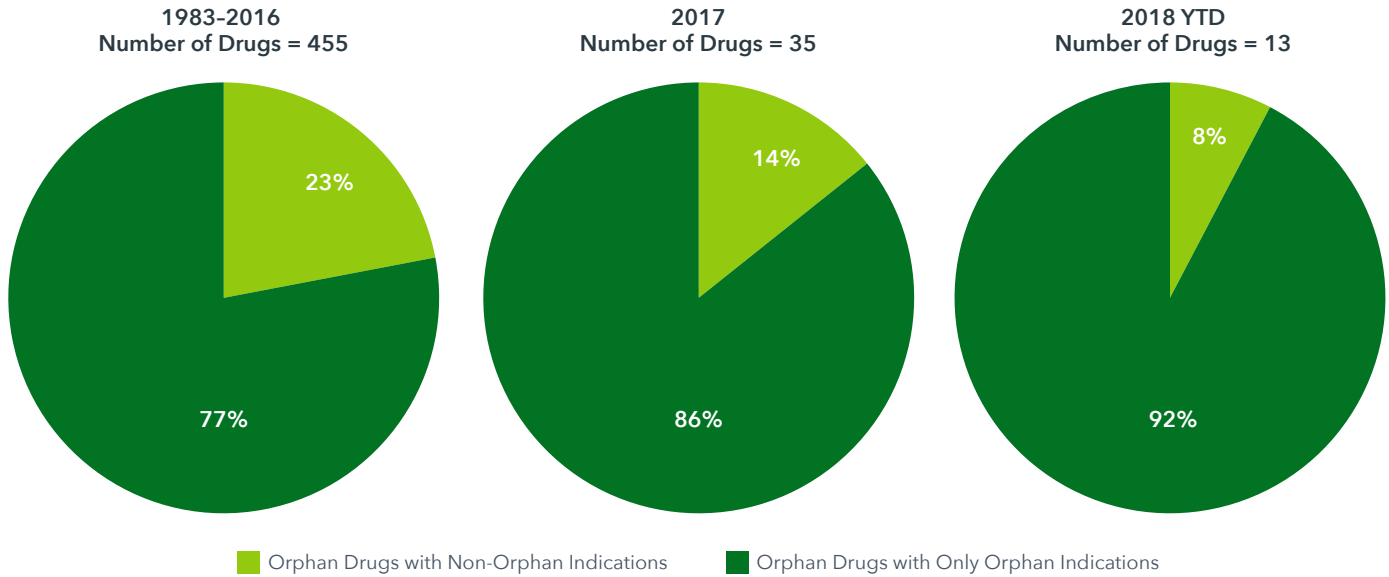
ORPHAN APPROVALS FOR NON-ORPHAN INDICATIONS

Of the 503 distinct drugs approved with any orphan indications since the passage of the Orphan Drug Act to August 2018, 394 (78%) drugs have been approved only for orphan indications and the remaining 109 drugs (22%) have approvals for both orphan and non-orphan indications (see Exhibit 9).

Of the 109 drugs with both orphan and non-orphan indications, 60 received a non-orphan indication first, while 36 received an orphan indication first, and 13 drugs received both orphan and non-orphan indications simultaneously (see Exhibit 10).

Among drugs with both orphan and non-orphan indications, some launched first with orphan-uses and others with non-orphan uses first. Several drugs with 2017 or 2018 orphan indication approvals also have current or prior non-orphan approvals (see Exhibit 11). Bevacizumab, first approved in 2004 has received ten indications, including five orphan indications. Overall orphan uses of this drug account for 9% of sales. Nivolumab and pembrolizumab, both immunology checkpoint inhibitors, launched initially in 2014 with orphan indications for melanoma, and received subsequent, non-orphan approvals such as non-small cell lung cancer. The percent of orphan sales for nivolumab and pembrolizumab in 2017 were 11.3% and 21.0%, respectively.

Exhibit 9: Orphan Drugs with and without Additional Non-Orphan Indications



Source: FDA Orphan Drug Database; Drugs@FDA Database, FDA websites, Sep 2018

Note: Total number of drugs 1983–2018 YTD=503; Counts distinct drugs approved with any orphan indication since the passage of the Orphan Drug Act. Includes drug approvals through Aug 2018.

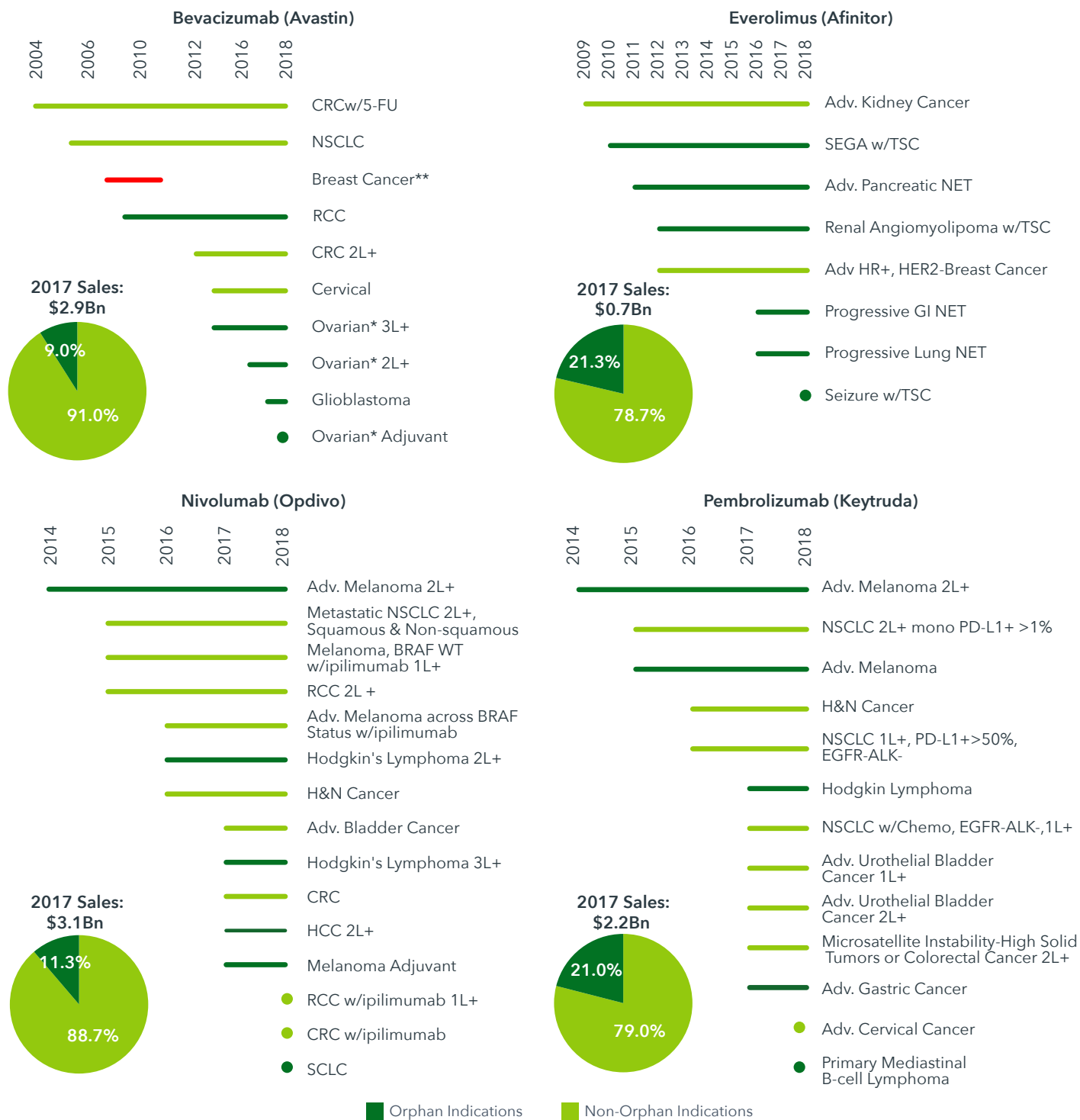
Exhibit 10: Number of Orphan Drugs Stratified by Approval Sequence

	1983-2016 Number of Drugs = 455	2017 Number of Drugs = 35	2018 YTD Number of Drugs = 13
Orphan Only	352	30	12
Non-Orphan Indication First	58	1	1
Orphan Indication First	35	1	
Orphan/Non-Orphan Simultaneous	10	3	

Source: FDA Orphan Drug Database; Drugs@FDA Database, FDA websites, Sep 2018

Note: Total number of drugs 1983–2018 YTD=503; Counts distinct drugs approved with any orphan indication since the passage of the Orphan Drug Act. Includes drug approvals through Aug 2018.

Exhibit 11: Orphan and Non-Orphan Approvals and Sales of Selected Drugs with 2017 Orphan Approvals



Source: IQVIA National Sales Perspectives, Jan 2018; IQVIA Pipeline Intelligence; FDA Orphan Drug Database; Drugs@FDA Database, FDA websites, Sep 2018
 Note: 1L+ = first-line; 2L+ = second-line; 3L+ = third-line; Adv. = advanced; CRC = colorectal cancer; 5FU = 5-Fluorouracil; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; SEGA = subependymal giant cell astrocytoma; TSC = tuberous sclerosis complex; NET = neuroendocrine tumor; HR+ = hormone receptor positive; HER2 = human epidermal growth factor receptor 2; H&N = head and neck; CRC = colorectal cancer; HCC = hepatocellular carcinoma; PD-L1 = programmed death-ligand 1; EGFR = epidermal growth factor receptor; ALK = anaplastic lymphoma kinase; * = Epithelial ovarian, fallopian tube, and primary peritoneal cancer are counted as one approval; ** = Approved for use in combination with paclitaxel in patients who have not received chemotherapy for metastatic HER2 negative breast cancer, but the approval was withdrawn in 2011.

Note: Medicine volume was measured in extended units, which are the smallest dose unit of a medicine such as pills, vials, across all types of drugs. This is a rough measure of volume which has a limitation that dissimilar items are not normalized to an equivalent volume. As a general indicator of how widely used medicines are, however, the metric shows how rarely orphan drugs are used. To segment drugs with both orphan and non-orphan uses, their volume has been split by indication (see Methodology for details).

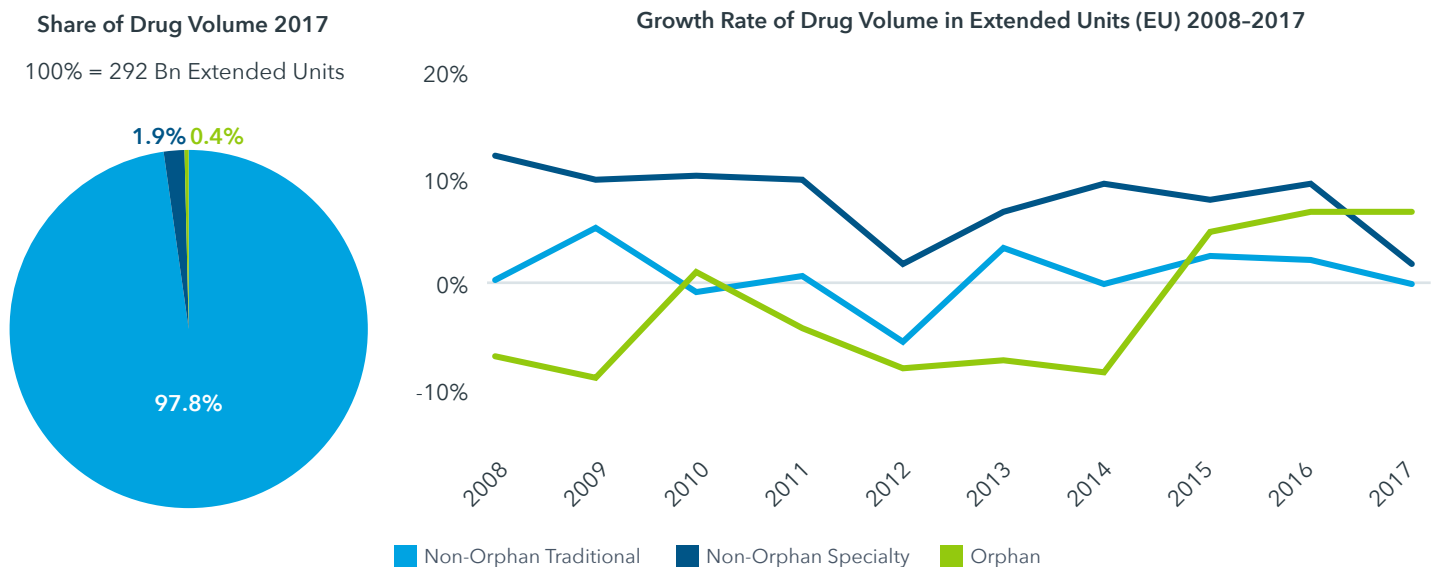
medicine varied widely; after 2004, the volume growth of orphan drugs began to consistently fall below non-orphan specialty and traditional medicines. Despite an increase in the number of orphan drugs available on the market, the total volume of orphan drugs (factored to reflect usage only for their orphan indications) has declined in most of the last ten years, though the last three years have shown positive growth (see Exhibit 12). The declining growth for orphan drugs has come in part from the shift to medicines which are dosed less frequently and to fewer patients, thus resulting in fewer doses as measured by extended units. Some other orphan drugs which were approved much earlier have seen less usage, as other treatments using fewer doses per patient have become more preferred.

VOLUME

In 2017, non-orphan traditional drugs accounted for 97.8% of the total volume of drugs sold and non-orphan specialty drugs accounted for an additional 1.9%. The remaining 0.4% of volume was the result of drugs used according to their orphan indications. From 1983 to 2004, the growth rates associated with each type of

This volume trend reflects lower use of some of the older and higher volume orphan drugs, such as metronidazole, balsalazide and midodrine. The orphan drug share of total volume has similarly declined from a peak of 0.6% in 2003 to just over 0.3% in 2014 and then rising to just under 0.4% in 2017 (see Exhibit 13).

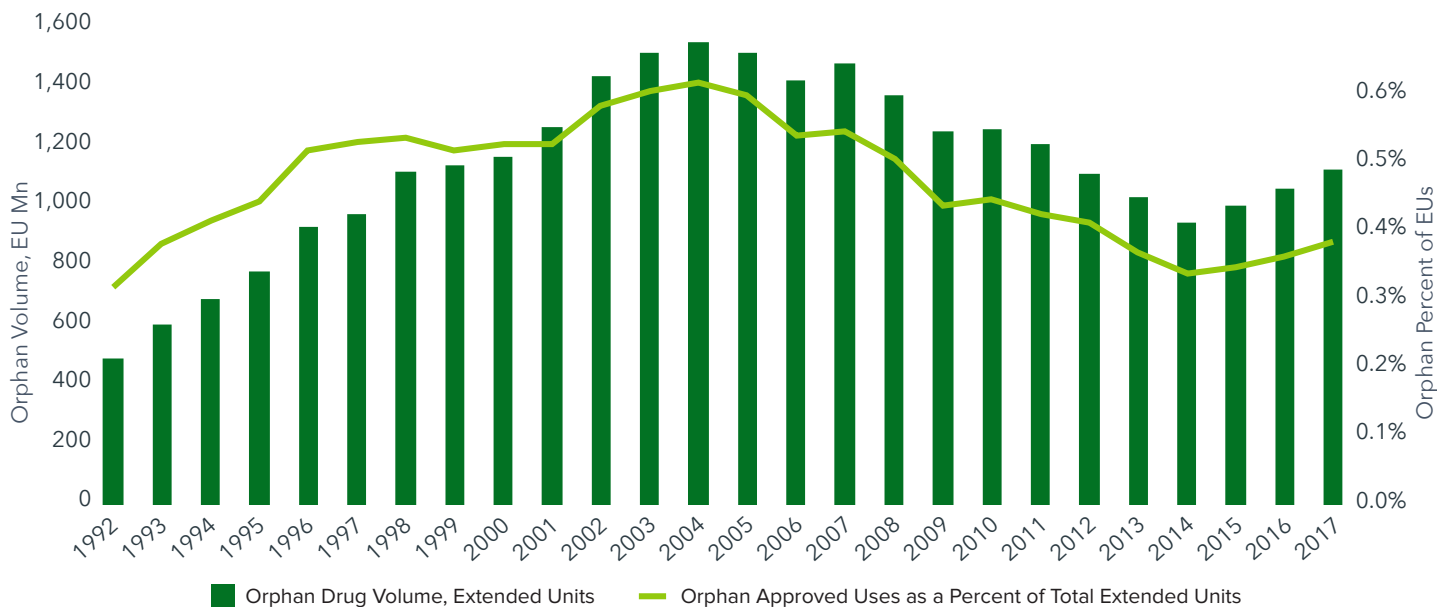
Exhibit 12: Trends in Traditional, Specialty and Orphan Drug Volume



Source: IQVIA National Sales Perspectives, Jan 2018; FDA Orphan Drug Database; Drugs@FDA Database, FDA websites, Sep 2018

ORPHAN DRUGS IN CONTEXT

Exhibit 13: Orphan Drug Volume and Share of Total Drug Volume in the United States 1993-2017



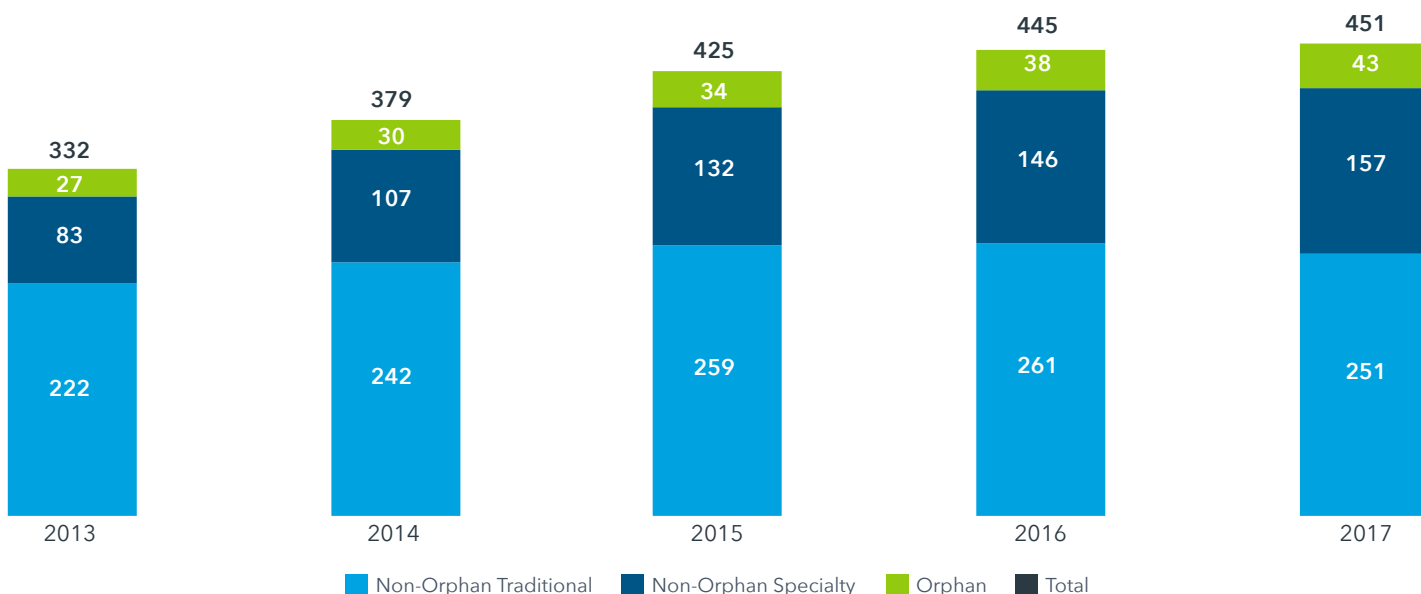
Source: IQVIA National Sales Perspectives, Jan 2018; FDA Orphan Drugs Database, Drugs@FDA Database, accessed Sep 2018; IQVIA Institute, Sep 2018

SALES

Orphan drugs represent less than 10% of spending. In 2017, the total drug sales in the United States was \$451 billion; 55.7% was from non-orphan traditional drugs,

while over one-third was spent on non-orphan specialty drugs (see Exhibit 14). The remaining 9.6% of spending – about \$43 billion – is attributed to the orphan indications of approved drugs (see Exhibits 14 and 15).

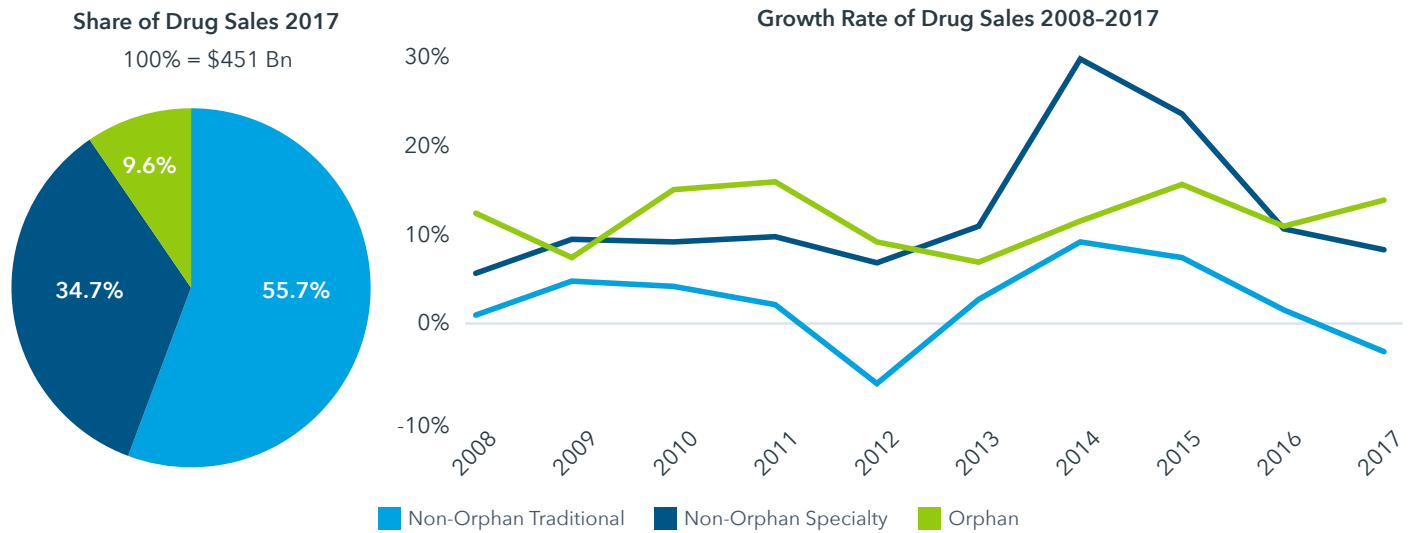
Exhibit 14: Total Drug Spending by Orphan, Traditional and Specialty in the United States, US\$Bn



Source: IQVIA National Sales Perspectives, Jan 2018; FDA Orphan Drug Database; Drugs@FDA Database, FDA websites accessed Sep 2018

Notes: Numbers may not sum to total due to rounding.

Exhibit 15: Trends in Traditional, Specialty and Orphan Drug Sales, US\$

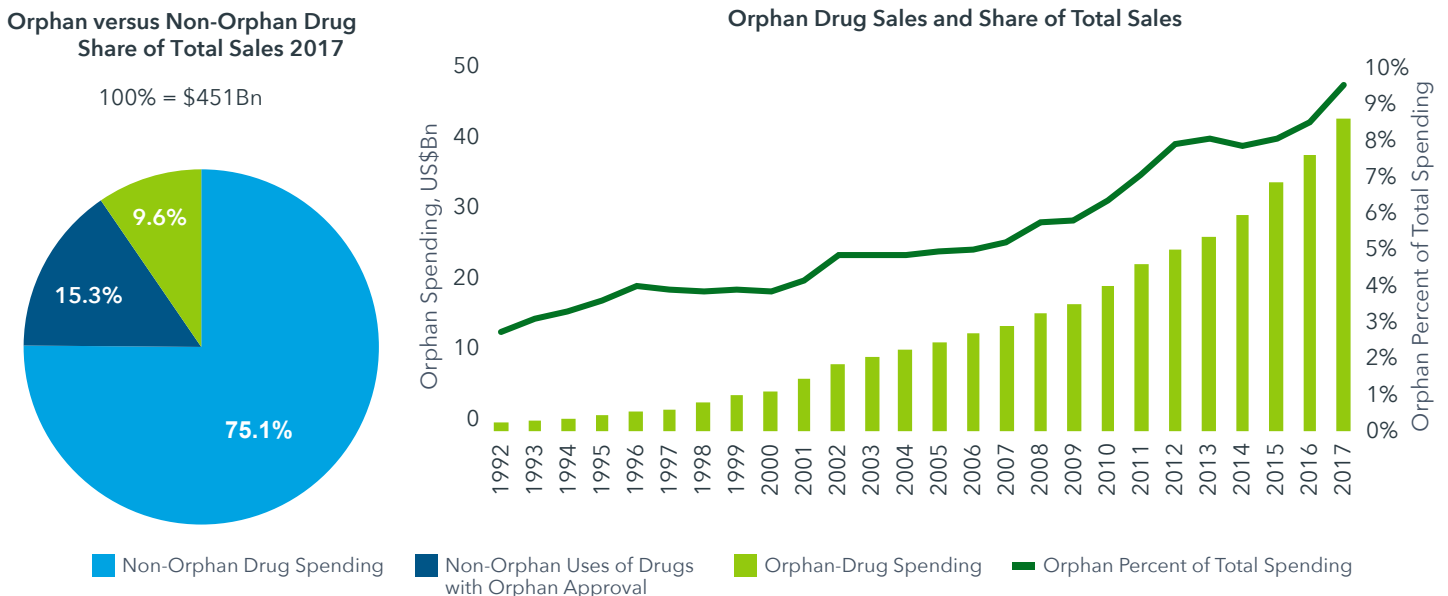


Source: IQVIA National Sales Perspectives, Jan 2018; FDA Orphan Drug Database; Drugs@FDA Database, FDA websites, Accessed Sep 2018

Spending growth rates have generally slowed for traditional medicines since the late 1990s while specialty and orphan drugs have grown more rapidly, with orphan drugs growing faster than other segments during the period 2008-2012 and again in 2017.

In 2014 and 2015, non-orphan specialty drug sales rose rapidly due primarily to the introduction of new hepatitis C treatments, bringing dramatic advances to those patients suffering from this disease.

Exhibit 16: Spending on Orphan Drugs in the United States, US\$

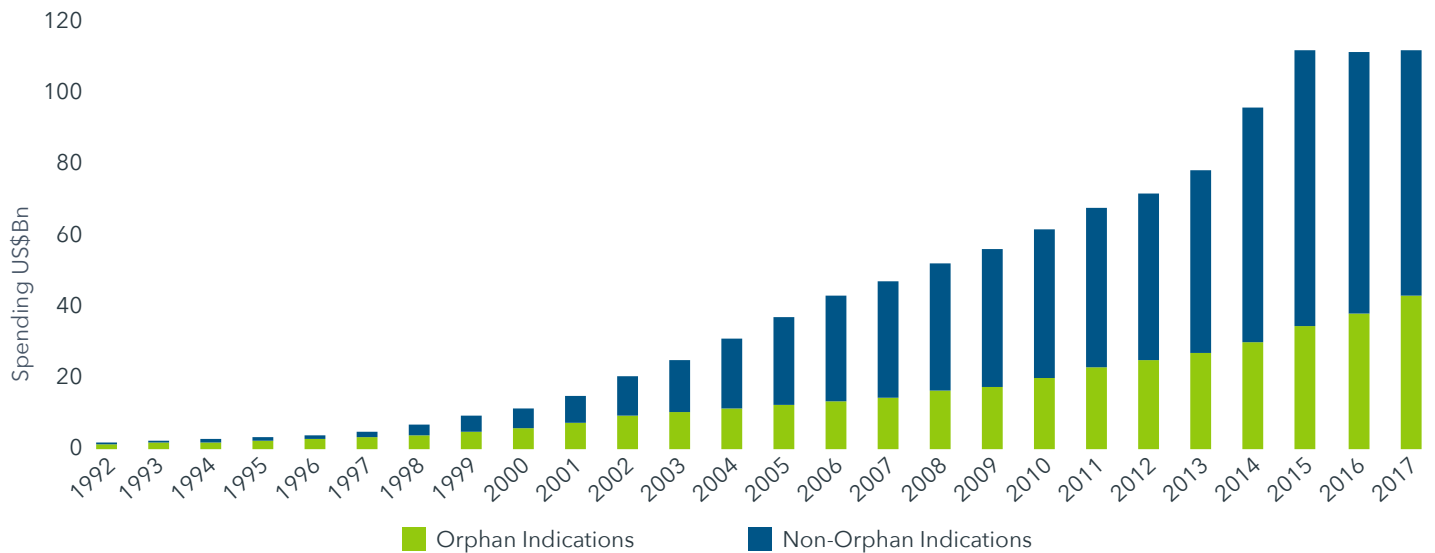


Source: IQVIA National Sales Perspectives, Jan 2018; FDA Orphan Drug Database; Drugs@FDA Database, FDA websites, Accessed Sep 2018

Note: Volume is based on Extended Units. Orphan drug spending includes only orphan approved uses of drugs with orphan approvals.

ORPHAN DRUGS IN CONTEXT

Exhibit 17: Spending on Orphan Drugs by Orphan and Non-Orphan Indications in the United States 1992-2017, US\$Bn

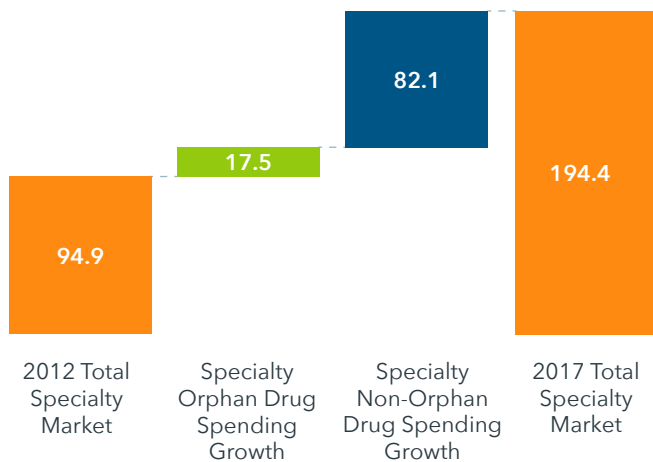


Source: IQVIA National Sales Perspectives, Jan 2018; FDA Orphan Drugs Database, Sep 2018; IQVIA Institute Sep 2018

Notes: The graphic represents sales of molecules with one or more orphan indications, split by sales of orphan indications and sales of non-orphan indications.

Orphan drugs represent an increasing number of the drugs available in the market, with concentrations in oncology, hemophilia and related blood disorders, and genetic disorders. While the number of orphan drugs has increased, overall spending has been increasing

Exhibit 18: Orphan Drug Contribution to Specialty Drug Spending Growth in the United States 2012-2017, US\$Bn



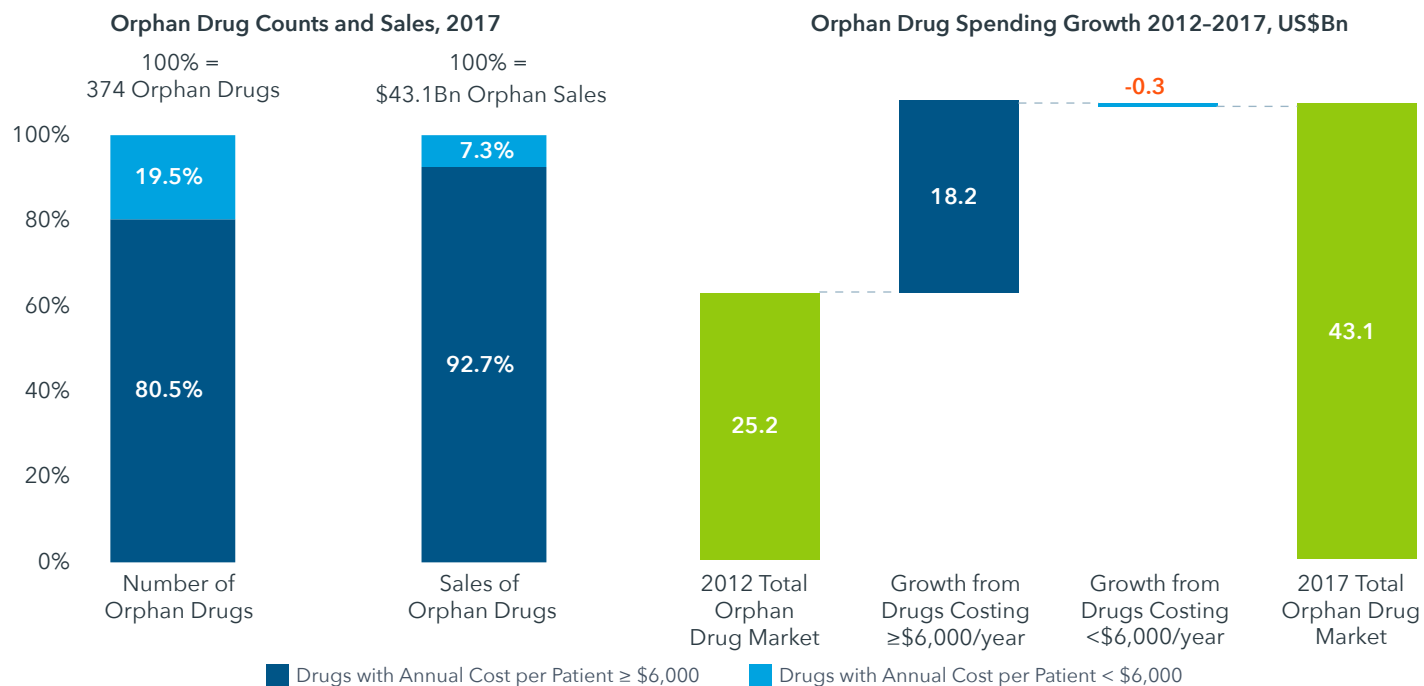
Source: IQVIA National Sales Perspectives, Jan 2018; FDA Orphan Drugs Database, Sep 2018; IQVIA Institute Sep 2018

more slowly. While non-orphan drug spending has shown some areas of decline in the past decade, orphan drug spending grew at an 11.4% CAGR over the past 10 years (Exhibit 15), compared to the total market at 4.9%.

During the past five years, while the number of approved orphan drugs increased from 364 in 2013 to 487 in 2017, the share of total drug spending tied to orphan indication use increased from 8.1% to 9.6% (see Exhibit 16), up from about 3% in 1993. Non-orphan use of these molecules represents 15.3% of overall medicines spending, reflecting that for those molecules with both orphan and non-orphan indications, the non-orphan indications represent much of their use and sales. Over time, the combined sales of both uses of these molecules have risen to over \$112 billion in 2017 or 24.9% of overall medicine spending.

However, the amount of those sales attributed to orphan indications accounts for just over one-third of spending among the drugs with any orphan indications/uses (see Exhibit 17).

Exhibit 19: Orphan Drug Counts, Spending and Growth by Annual per Patient Cost



Source: IQVIA National Sales Perspectives, Jan 2018; FDA Orphan Drugs Database, accessed Sep 2018; IQVIA Institute, Sep 2018

DRUGS WITH AN ANNUAL COST PER PATIENT OF:	DRUG THERAPY CLASS	COUNT OF PRODUCTS	2017 SHARE OF TOTAL ORPHAN SALES
<\$6,000	CNS	2	4.2%
	Urological	3	0.7%
	Blood coagulation	3	0.7%
	Antiparasitics/antimalarials/insecticides	5	0.4%
	Parkinson's and epilepsy	3	0.3%
	Anti-anaemics, iron and all combinations	2	0.2%
	Respiratory	3	0.2%
	Pain	4	0.2%
	Gastrointestinal	4	0.1%
	Cardiovascular	5	0.1%
	All others	39	0.3%
	>\$6,000	Oncologics	109
Multiple sclerosis		4	13.3%
Respiratory		5	5.7%
Autoimmune diseases		5	5.3%
Cardiovascular		11	3.7%
Alimentary tract and metabolism		19	2.6%
Nervous system disorders		8	2.6%
Blood coagulation		16	2.0%
Immunosuppressants for organ transplants		8	1.6%
Growth hormones		5	1.5%
All others		111	13.7%

Source: IQVIA National Sales Perspectives, Jan 2018; FDA Orphan Drugs Database, accessed Sep 2018; IQVIA Institute, Sep 2018

Note: CNS includes ATC codes for psycholeptics, psychoanaleptics and other nervous system drugs.

ORPHAN DRUGS IN CONTEXT

ORPHAN DRUG CONTRIBUTION TO SPENDING GROWTH

Over the past five years, growth in spending from specialty drugs has drawn significant attention. These include drugs for the treatment of cancer, autoimmune disorders and HIV/AIDS, multiple sclerosis and viral hepatitis. Growth in spending of these drugs is primarily due to the approval and availability of new treatments and an increased number of patients receiving these medicines. Over the five-year period, total spending on specialty drugs has almost doubled, from \$94.9 billion to \$194.4 billion: an increase of \$99.5 billion. Specialty orphan drugs contributed about \$17.5 billion of growth—with non-orphan specialty drugs contributing the remaining \$82.1 billion of growth over the five-year period (see Exhibit 18).

Within the orphan drug segment, most of the drugs, spending, and growth in spending comes from

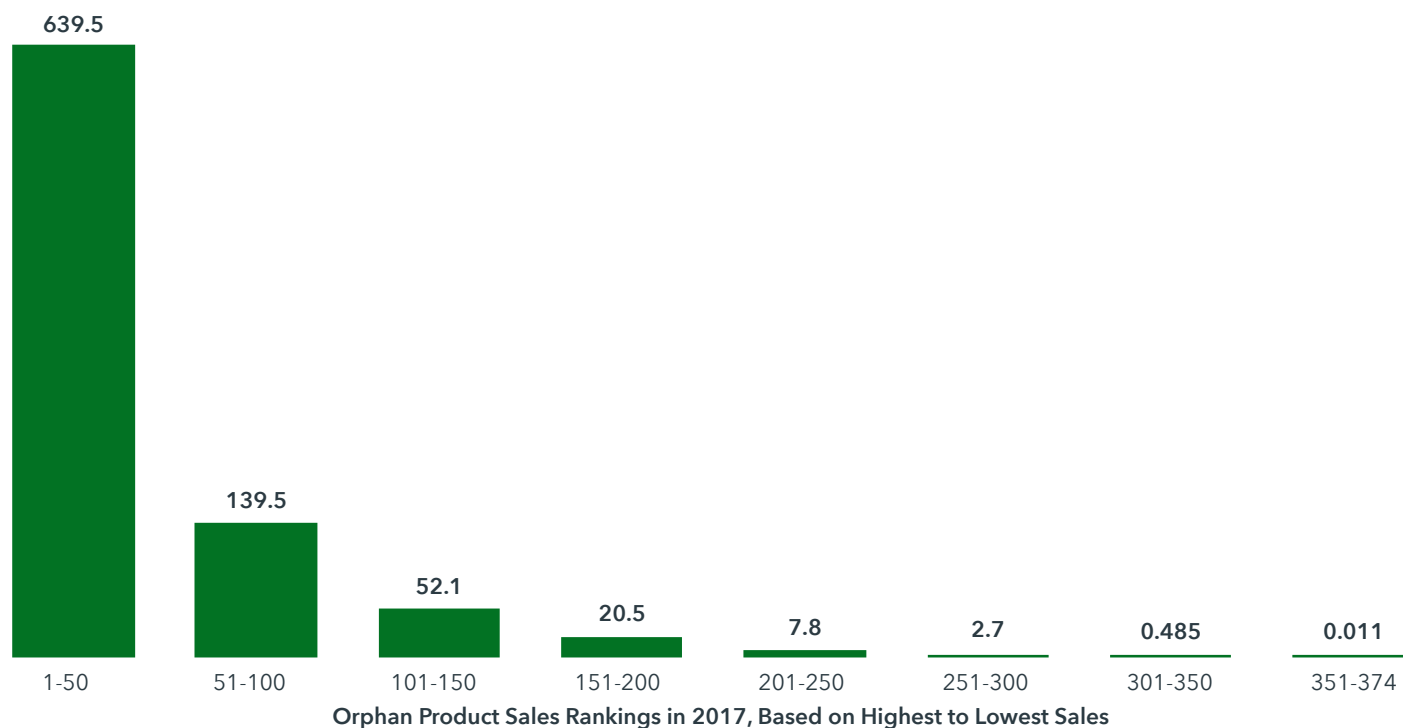
medicines with annual costs in excess of \$6,000. In 2017, these drugs represented over 80% of the drugs and 92.7% of total sales, as well as the vast majority of growth in orphan drug spending (see Exhibit 19).

AVERAGE SALES AND PRICE OF ORPHAN DRUGS

Among the cohort of drugs with one or more orphan designations, there is wide variation in pricing and annual sales of individual products. In some cases, these drugs are sold to a very small numbers of patients (less than 1,000) while in others, the number of patients receiving the drug can reach several hundred thousand (across multiple indications).

In 2017, the 50 highest-selling orphan products had average sales for the year of \$639.5 million. The next 50 highest-selling products averaged \$139.5 million, followed by \$52.1 million for the subsequent 50. The remaining 300 orphan drugs averaged much lower average sales (see Exhibit 20).

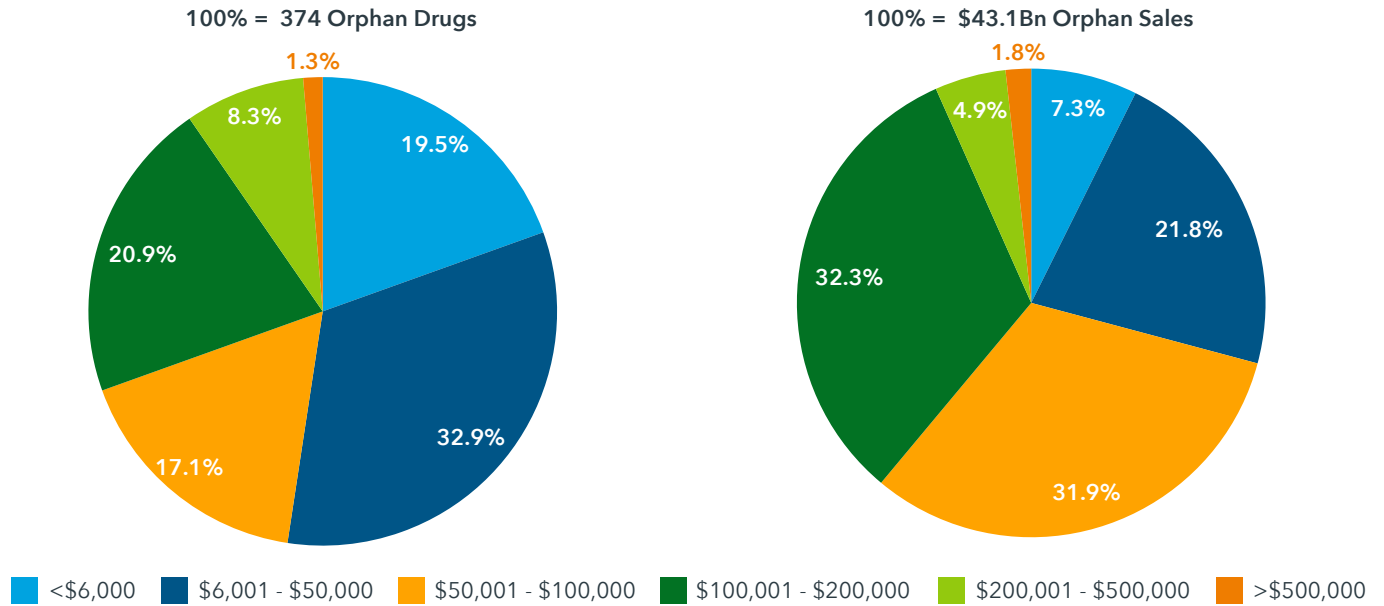
Exhibit 20: Average Orphan Product Sales per 50-Product Group Ranked from Highest to Lowest Sales, US\$Mn



Source: IQVIA National Sales Perspectives, Jan 2018; FDA Orphan Drugs Database, accessed Sep 2018; IQVIA Institute, Sep 2018

Note: Product 1 has the highest 2017 sales value in the United States among the 374 products.

Exhibit 21: Orphan Drug Counts and Sales by Annual per Patient Cost in the United States in 2017



Source: IQVIA National Sales Perspectives, Jan 2018; FDA Orphan Drugs Database, accessed Sep 2018; IQVIA Institute, Sep 2018

The annual cost per patient for orphan drugs also varies widely. About 20% of the drugs (n=73) are priced at less than \$6,000 per year, and they contribute 7.3% of total spending on orphan drugs. About 1.3% of orphan drugs are priced in excess of \$500,000 per year (n=5), but they only account for 1.8% of orphan drug spending due to relatively few patients being treated with these medicines (see Exhibit 21). Examples include Actimmune, Brineura and Soliris.

Notes on sources

THIS REPORT IS BASED ON THE IQVIA SERVICES DETAILED BELOW

National Prescription Audit (NPA)™ is a suite of services that provides the industry standard source of national prescription activity for all products and markets.

National Sales Perspectives (NSP)™ measures spending within the U.S. pharmaceutical market by pharmacies, clinics, hospitals and other healthcare providers. NSP reports 100% coverage of the retail and non-retail channels for national pharmaceutical sales at actual transaction prices. The prices do not reflect off-invoice price concessions that reduce the net amount received by manufacturers.

“SMART - Launch Edition” is a service that allows users to study the market uptake and launch criteria, both of the marketplace and product, for branded and generic launches from 1992 to present-day.

IQVIA MIDAS™ is a unique data platform for assessing worldwide healthcare markets. It integrates IQVIA national audits into a globally consistent view of the pharmaceutical market, tracking virtually every product in hundreds of therapeutic classes and providing estimated product volumes, trends and market share through retail and non-retail channels. MIDAS data is updated monthly and retains 12 years of history.

IQVIA Formulary Impact Analyzer (FIA) provides insight into what impact utilization-control measures enforced by managed care organizations have had on prescription volumes including the dynamics that affect patient behavior in filling and/or refilling prescriptions. Formulary measures include tiered copay benefit designs, prior authorization restrictions, and often result in non-preferred prescriptions being rejected or switched at the pharmacy. FIA offers visibility to claims rejected for other reasons such as contraindications as well as those attempted to be refilled too soon. FIA sources include national and regional chains, independent pharmacies and a claims coordination switch company providing a comprehensive view of retailers and across geographies.

Methodology

STUDY DATA AND METHODS

The FDA's Orphan Drug Product designation database was used to identify a comprehensive list of drugs that were approved by the FDA and given orphan status between passage of the Orphan Drug Act in 1983 through August 2018.⁴ We used the IQVIA SMART US Launch edition database to assess U.S. invoice-price revenues on all drugs and on orphan drugs in the period 1992–2017 (at the time of the analysis, 2017 was the last year for which full data were available). The 503 unique brand-name orphan drugs that had been approved in the United States from 1983 through August 2018 were identified from the FDA's Orphan Drug Product designation database. Where a medicine had multiple orphan designations, this was noted for analysis of orphan and non-orphan designation approval time sequence analysis, and for the application of factors to estimate orphan uses of the drugs. Each orphan drug with multiple dosage formulations is counted only once, aggregating the formulations. According to the FDA, orphan drug designation is conferred on the active moiety, or principal molecular structure, instead of on the formulation.³² The Drugs@FDA database, which includes information on approved drug products and approval history, was used to identify all approved indications for orphan drugs and approval dates. The IQVIA SMART US Launch Edition database was used to identify sales of the orphan drugs, and to include data from 1992–2017 as the most complete archive available. The database accurately summarizes estimated product volumes and sales by product and therapy class through retail and non-retail channels. All volume data and associated drug sales for products included in this study were validated by IQVIA's data integrity team.

PARTIAL ORPHAN DRUGS

Since the FDA may approve a drug for multiple indications, we undertook a further evaluation to identify "partial orphan drugs," products with both orphan and non-orphan indications. Of the 503 orphan drugs designated by the FDA, 109 had both orphan and non-orphan approved indications. Because the IQVIA sales data are not segmented by indication, an in-depth analysis was conducted of the partial orphan drugs to determine a "disease" factor to apply to the expenditures of each drug, with the goal of isolating and segmenting orphan uses from non-orphan uses of the drugs. To conduct this analysis, we consulted several U.S. sources to determine the sizes of the different disease populations and factor the sales and volume data. These sources included the March 2018 Cowen and Company Therapeutic Categories Outlook report, manufacturers' audited financial reports, published epidemiology estimates (incidence or prevalence rates) for the United States, medical claims data, or office-based physician diagnosis surveys collected in IQVIA National Disease and Therapeutic Index (NDTI).³³ The disease factor from the most robust source (taking into account sample size— that is, number of claims; setting of care; and so on) out of all available sources was applied to the total product expenditures of a given drug to measure spending associated with orphan indications only. Approval dates for orphan and non-orphan indications were considered as applicable (the disease factors used have varied across years – for example, an orphan drug might have been approved for an orphan indication only in 2008 and then for a non-orphan indication in 2011, so the disease factor would be 100% orphan from 2008–2010 and then factored to reflect the mix of orphan and non-orphan uses from 2011).

Methodology

LIMITATIONS

IQVIA database coverage may be subject to limitations where volumes are low or distributed through limited wholesaler or pharmacy networks and some product sales may be understated for lower volume products, which could include orphan drugs. Nevertheless, sales data are estimated to represent 98 percent of overall sales in the United States. Factoring sales data by epidemiology, claims or reported diagnosis data are all less robust methods than recording exact sales values. Products with only orphan indications represent a more reliable measure of orphan spending as they are not adjusted by these factors.

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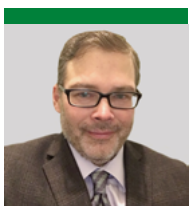
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Murray Aitken is Executive Director, IQVIA Institute, which provides policy setters and decision-makers in the global health sector with objective insights into healthcare dynamics. He led the IQVIA Institute for Human Data Science (formerly the IMS Institute for Healthcare Informatics) since its inception in January 2011. Murray previously was Senior Vice President, Healthcare Insight, leading IMS Health's thought leadership initiatives worldwide. Before that, he served as Senior Vice President, Corporate Strategy, from 2004 to 2007. Murray joined IMS Health in 2001 with responsibility for developing the company's consulting and services businesses. Prior to IMS Health, Murray had a 14-year career with McKinsey & Company, where he was a leader in the Pharmaceutical and Medical Products practice from 1997 to 2001. Murray writes and speaks regularly on the challenges facing the healthcare industry. He is editor of Health IQ, a publication focused on the value of information in advancing evidence-based healthcare, and also serves on the editorial advisory board of Pharmaceutical Executive. Murray holds a Master of Commerce degree from the University of Auckland in New Zealand, and received an M.B.A. degree with distinction from Harvard University.



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About the IQVIA Institute

The IQVIA Institute for Human Data Science contributes to the advancement of human health globally through timely research, insightful analysis and scientific expertise applied to granular non-identified patient-level data.

Fulfilling an essential need within healthcare, the Institute delivers objective, relevant insights and research that accelerate understanding and innovation critical to sound decision making and improved human outcomes. With access to IQVIA's institutional knowledge, advanced analytics, technology and unparalleled data the Institute works in tandem with a broad set of healthcare stakeholders to drive a research agenda focused on Human Data Science including, including government agencies, academic institutions, the life sciences industry and payers.

Research Agenda

The research agenda for the Institute centers on 5 areas considered vital to contributing to the advancement of human health globally:

- Improving decision-making across health systems through the effective use of advanced analytics and methodologies applied to timely, relevant data.
- Addressing opportunities to improve clinical development productivity focused on innovative treatments that advance healthcare globally.
- Optimizing the performance of health systems by focusing on patient centricity, precision medicine and better understanding disease causes, treatment consequences and measures to improve quality and cost of healthcare delivered to patients.

- Understanding the future role for biopharmaceuticals in human health, market dynamics, and implications for manufacturers, public and private payers, providers, patients, pharmacists and distributors.
- Researching the role of technology in health system products, processes and delivery systems and the business and policy systems that drive innovation.

Guiding Principles

The Institute operates from a set of Guiding Principles:

- Healthcare solutions of the future require fact based scientific evidence, expert analysis of information, technology, ingenuity and a focus on individuals.
- Rigorous analysis must be applied to vast amounts of timely, high quality and relevant data to provide value and move healthcare forward.
- Collaboration across all stakeholders in the public and private sectors is critical to advancing healthcare solutions.
- Insights gained from information and analysis should be made widely available to healthcare stakeholders.
- Protecting individual privacy is essential, so research will be based on the use of non-identified patient information and provider information will be aggregated.
- Information will be used responsibly to advance research, inform discourse, achieve better healthcare and improve the health of all people.

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