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DECEMBER 2018

Orphan Drugs in the United States

Exclusivity, Pricing and Treated Populations

Introduction

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In the thirty-five years since the passage of the Orphan Drug Act (ODA) in 1983, the structure of development incentives laid out in the legislation has successfully spurred investment and innovation in rare disease therapies. Still, approximately 95% of the 7,000 rare diseases remain without any therapeutic options. Recent legislative discussion has focused on whether the ODA development incentives are working as intended or whether they are being manipulated for commercial gain. In this regard, it is particularly important to understand whether the orphan designations granted have delayed generic competition. There has also been significant attention focused on the pricing of orphan drugs both at launch and over time. A persistent issue—with implications for both the pricing and levels of commercial support needed for these drugs—remains that rare disease patients are difficult to diagnose, and as a result, available treatments have limited use by only a small proportion of patients with confirmed disease.

This report is a companion analysis to an examination of the orphan drug market published by the IQVIA Institute in October 2018, "Orphan Drugs in the United States: Growth Trends in Rare Disease Treatments," and brings a new perspective on the sequence of orphan and non-orphan indications approved and their associated patent and market exclusivities. It also examines orphan drug pricing relative to patient numbers and how those prices change over time. In a first-of-its-kind comprehensive analysis, the report compares current disease epidemiology to the number of treated patients to demonstrate the challenges in bringing orphan drugs to patients even after they're approved. Overall, these analyses bring critical and updated information to the understanding of orphan drugs in the United States.

The research in this report was undertaken independently by the IQVIA Institute, with funding from the National Organization for Rare Disorders (NORD). 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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NORD® National Organization for Rare Disorders

This report was produced with funding from the National Organization for Rare Disorders (NORD)

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Executive summary

One of the key aspects of the Orphan Drug Act of 1983 is a seven-year market exclusivity granted to drugs that treat rare diseases. In the thirty-five years since the passage of the Orphan Drug Act, a total of 503 drugs have received orphan status from the FDA. Of these, 217 drugs are now no longer protected by either orphan designations or patents, and yet only 116 of these unprotected medicines currently face generic or biosimilar competitors. Notably, just over half of the unprotected products have faced competition, even decades after the lapsing of exclusivity.

In practice, the explicit orphan exclusivity has only rarely been the factor which has delayed generic or biosimilar competitors. Orphan exclusivity was in effect longer than patent protection for only 60 of the 503 drugs that have received orphan status (see Methodology). Thus, it is most often the lapse of patent exclusivity that enables competition and not the orphan drug exclusivity (ODE). Of note, it appears that the practical aspects of developing and manufacturing drugs for these populations has largely discouraged competitors. For instance, the median annual spending on those expired orphan drugs not facing competition was $8.6 million in 2017 reflecting very limited commercial opportunities for potential generic challengers. Of these 101 drugs, 30 have additionally been discontinued, suggesting that these medicines were either made less relevant by subsequent innovations or were simply not profitable enough to continue.

Considering orphan designations mandate exclusive market opportunities, the pricing decisions of developers are of particular interest, especially with the recent string of high-profile approvals of orphan drugs with costs in the hundreds of thousands of dollars. In our earlier report,[1] an inverse relationship between high price and the number of patients treated was noted. Confirming this point, most orphan drugs were seen to have relatively low prices, and those that do have exceptionally high prices, also treat very few patients. In addition to launch prices, the ongoing pricing actions by manufacturers are of interest, and analysis shows that companies have consistently raised prices for orphan drugs more slowly than other branded drugs in the market. This has been demonstrated both historically as well as in a time-aligned comparison relative to the addition of orphan status for a drug. Compared to the orphan drug market as a whole, spending on those unprotected orphan drugs not experiencing generic competition can be considered modest, with drugs on average reaching just over $100 million in 2017 after approximately 10 years without a competitor. While there are some orphan drugs in this category which have more than $200 million in spending, they each have some unique circumstances relevant to delayed or absent competition. The highest spending drug in this group was Epogen, where biosimilar applications had been pending for some time and the first was launched in November 2018. Excluding the eight drugs with the greatest spending, the average spending on orphan brands not experiencing generic competition drops to just over $22 million in 2017 and an average 10.5 years without competition since the end of prior patent or orphan exclusivities.

These aspects of competition and pricing are an important reminder that the number of patients receiving a treatment is critical to both generating competition and supporting the sustainability of a market. A comprehensive epidemiological examination of 539 diseases that have approved orphan drugs further indicates that treated patients represent approximately 10% of disease prevalence for these rare diseases, with notable variability around this mean. In almost every circumstance, orphan drugs target fewer than 200,000 patients, though the actual target populations vary significantly, and the understanding of the number of patients with a disorder can evolve

over time. Poorly diagnosed diseases can become easier to identify if a new diagnostic is developed, and the wide adoption of genetic testing has helped improve identification for a range of inherited diseases. Additionally, awareness of a disease can be linked to the availability of a treatment option, and that awareness can encourage patients to seek treatment. Still, even in the presence of effective treatments, some rare diseases see fewer than 1% of their prevalent patients receiving orphan medicines given that diagnosis and treatment of rare diseases with very small populations remains complicated. This demonstrates the need for a concerted effort, once a drug is approved, to disseminate treatment guidance to the wider medical community and to patients. These efforts may take years even in optimal circumstances, and if patients do not receive a diagnosis, there is little that can be done. Lastly, these data suggest a stubborn analytical issue, which is that both the treated-patient estimates and epidemiology estimates are highly subject to the vagaries of multiple researchers working separately on specific studies without coordination. There are no comprehensive and definitive patient registries for many rare diseases, and it remains challenging to identify the size of a very rare patient population with confidence.

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
- **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
- **Orphan Drug Exclusivity (ODE)** refers to a seven-year market exclusivity from competitors for that medicine specifically for the designated orphan use. The exclusivity does not preclude generic competition for non-orphan approved uses of that drug. For additional information on other types market exclusivity and patent protection, see Methodology
- **Patent (and other exclusivities)** are those exclusivities granted to products by patents or 505(b)(2) approvals which delay, or are expected to delay, market entry of competitors. For additional information, see Methodology
- **Treated patients** are an estimate of the number of patients treated in a year with the orphan drug based on spending, approved dosing, cost per dose and proportion of usage for the relevant indication
- **Prevalence** refers to the proportion of the population who have a specific disease within a given time period
- **Incidence** refers to the occurrence of new cases of a disease within the population within a given time period

Orphan and patent exclusivity for orphan drugs

- Of all 503 drugs which have received orphan designations, 217 are now no longer protected by either orphan exclusivity or patent designations, but only 116 of these currently face generic competitors.
- As of June 2018, there were 101 medicines with lapsed exclusivity or patent protection not experiencing generic competition, in some cases, for many years.
- The median annual spending of these medicines was $8.6 million in 2017 reflecting very limited commercial opportunities for potential generic challengers.
- The remaining 286 drugs with orphan designations are still protected from generic competition by either orphan or patent exclusivities or both.
- The exclusivity granted to orphan drugs provides seven years without generic competition for the approved orphan designation but does not prevent generic competition for other approved uses of the medicine.
- Orphan exclusivity continues longer than patent protection in only 60 of the 503 orphan-designated medicines.
- When an orphan-designated drug receives approval, the duration of protected status is often longer than seven years, as patent protection often extends beyond orphan market exclusivity.

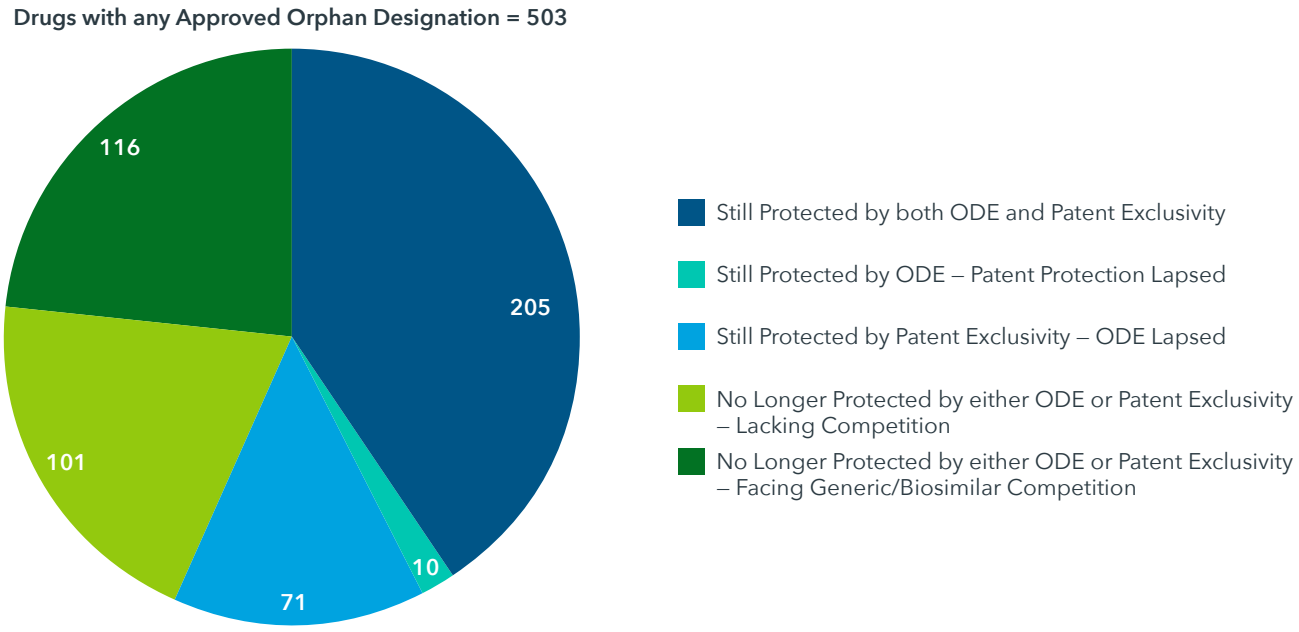
One of the more often cited but least understood aspects of the Orphan Drug Act is the market exclusivity it grants. With orphan designation, the FDA grants a seven-year market exclusivity for that medicine that applies specifically to that designated orphan use, but this exclusivity does not preclude generic competition for other non-orphan approved uses of that drug, nor for orphan uses for which the exclusivity has expired. To best understand the effective market exclusivity of orphan drugs, it is necessary to examine both the timing of orphan designations and the timing of patents and other market exclusivities (e.g., pediatric or other exclusivities) for those drugs.

Of the 503 distinct drugs to have ever received orphan designations for one or more indications since 1983, 286 remain protected by some form of exclusivity, either ODE or patent exclusivity (see Exhibit 1). Of those 217 that are no longer protected, generics are available in the market for 116 of them, while no competitors exist for 101 of them. The medicines currently facing generic competition can provide a view of the total duration of protection provided by both patent and ODE protections. Those not yet facing competition are indicative of challenges that delay the number of generic challengers, such as small-revenue markets.

The median spending for an orphan drug without market protection and not facing generic competition was $8.6 million in 2017 (see Exhibit 2).

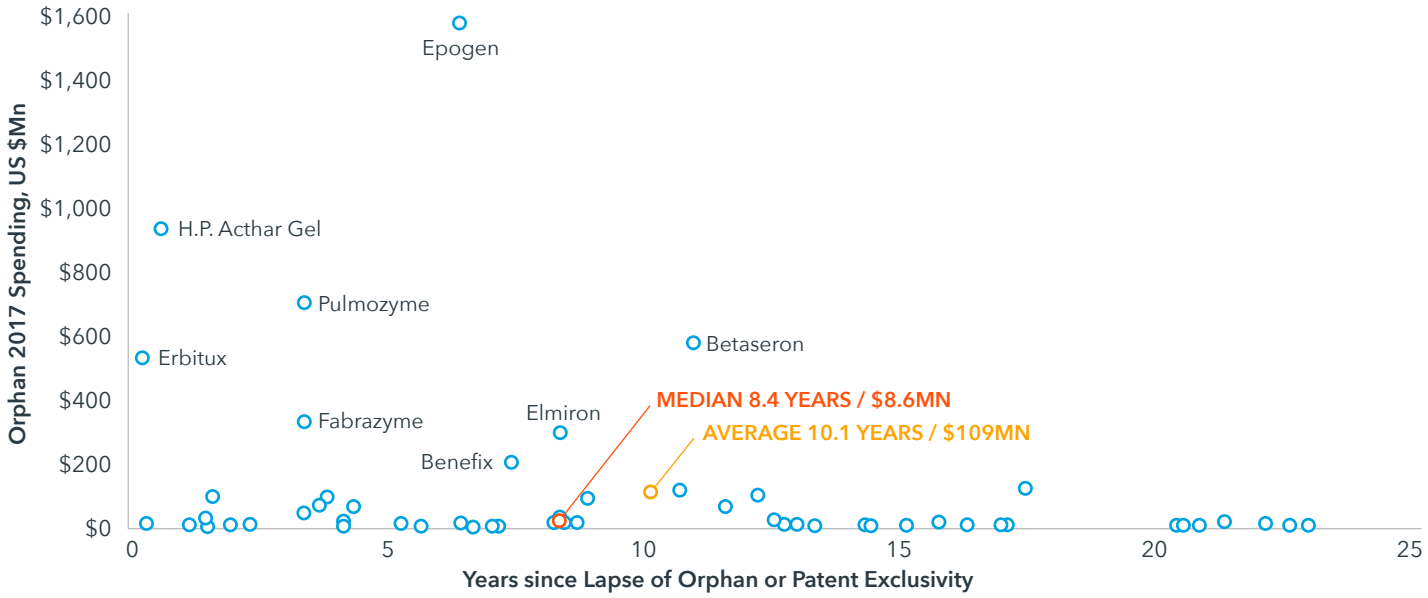
ORPHAN AND PATENT EXCLUSIVITY FOR ORPHAN DRUGS

Exhibit 1: Current Status of Patent Protection and Orphan Drug Exclusivity for Orphan Designated Drugs



Source: FDA Orphan Drugs Database, FDA Orange Book, Accessed Sep 2018; IQVIA ARK Patent Intelligence, IQVIA National Sales Perspectives, Oct 2018; IQVIA Institute; Nov 2018
Notes: ODE = Orphan drug exclusivity; patent protection includes other forms of market exclusivity (e.g., pediatric extension, 505(b)(2)). The 101 therapies no longer protected by either ODE or patent exclusivity did not have generic competitors as of June 2018. The 116 therapies no longer protected by either ODE or patent exclusivity currently have one or more generic or biosimilar competitors in the market.

Exhibit 2: Spending on Orphan Drugs No Longer Protected by Either Orphan Drug Exclusivity or Patent Protection



Source: FDA Orphan Drugs Database, FDA Orange Book, Accessed Sep 2018, IQVIA ARK Patent Intelligence, IQVIA National Sales Perspectives, Oct 2018; IQVIA Institute Nov 2018
Notes: ODE = Orphan drug exclusivity; patent protection includes other forms of market exclusivity (e.g., pediatric extension, 505(b)(2)). Orphan drugs shown have no remaining exclusivity and no current generic/biosimilar challengers by 2017. Excluding the top eight therapies in spending, the average years since lapse of orphan or patent exclusivity was 10.5 years and average spending was $22.1 million.

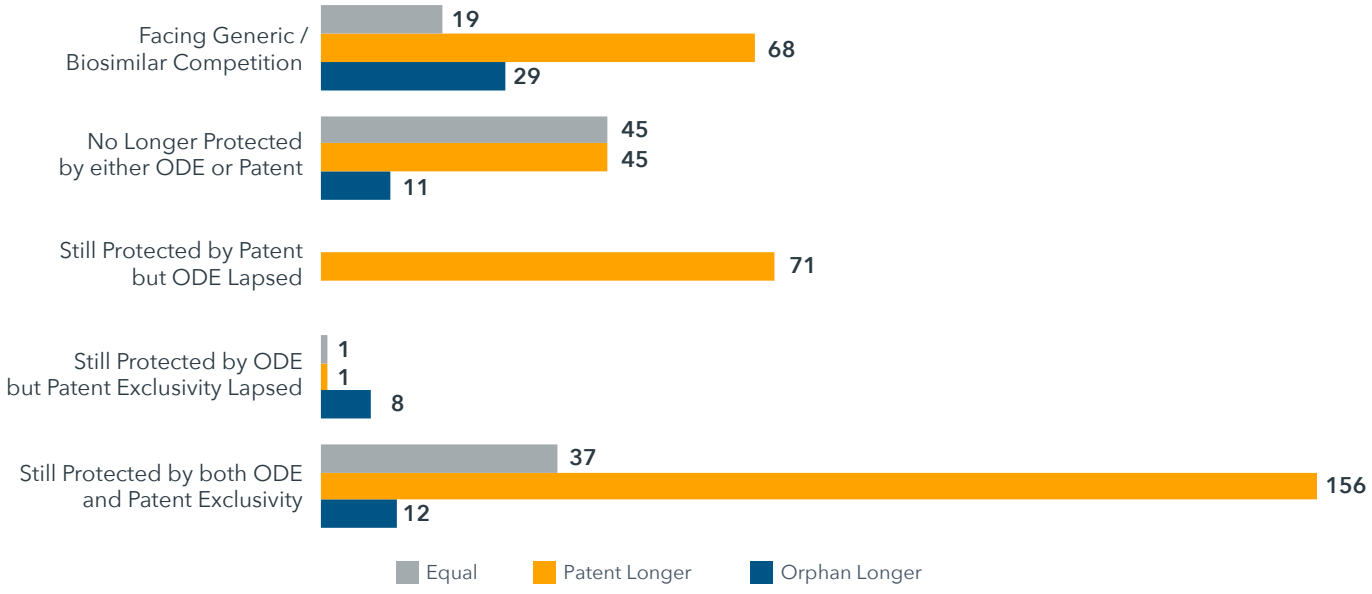
ORPHAN AND PATENT EXCLUSIVITY FOR ORPHAN DRUGS

While there is one drug in this category with more than $1 billion in spending, there are another seven with more than $200 million in spending, each of which have a unique circumstance which appears relevant to delayed or absent competition. Epogen (epoetin alfa), for example, has for some time been subject to pending biosimilar applications, the first of which was approved in November 2018. H.P. Acthar Gel (repository corticotropin injection) was first approved in the 1950s and through a series of reformulations is effectively protected by trade secrets around the manufacture of its formulation rather than by patents. Drugs for multiple sclerosis (MS) such as Betaseron (interferon beta-1b) could be subject to ongoing biosimilar applications but are not facing current competition, likely due to the complexity of the biosimilar regulatory pathway for interferon-based therapies and because of the greater commercial opportunities for newer branded MS drugs.

Aside from the eight largest-selling drugs in this group, all had 2017 sales below $120 million and averaged just over $22 million. The median time these drugs have been unprotected and without generic competition is 8.4 years. For most orphan medicines, particularly those with complex or costly manufacturing, and with less than $20 million dollars in annual sales, it is likely that they will never face generic or biosimilar competition. Many of these unprotected orphan drugs were launched more than a decade ago and to the extent to which they are still used in clinical practice – they will likely remain the only treatment option without generic competitors in perpetuity, or until a manufacturer ceases to produce them.

Additionally, since the passage of the Orphan Drug Act, only 12% (60 of 503) of orphan drugs have had greater exclusivity from their orphan status than from relevant patents, both historically and projected, for current orphan drugs (see Exhibit 3).

Exhibit 3: Number of Orphan Drugs by their Current Exclusivity Status and the Relative Duration of Their Orphan Drug Exclusivity and Patent Protection



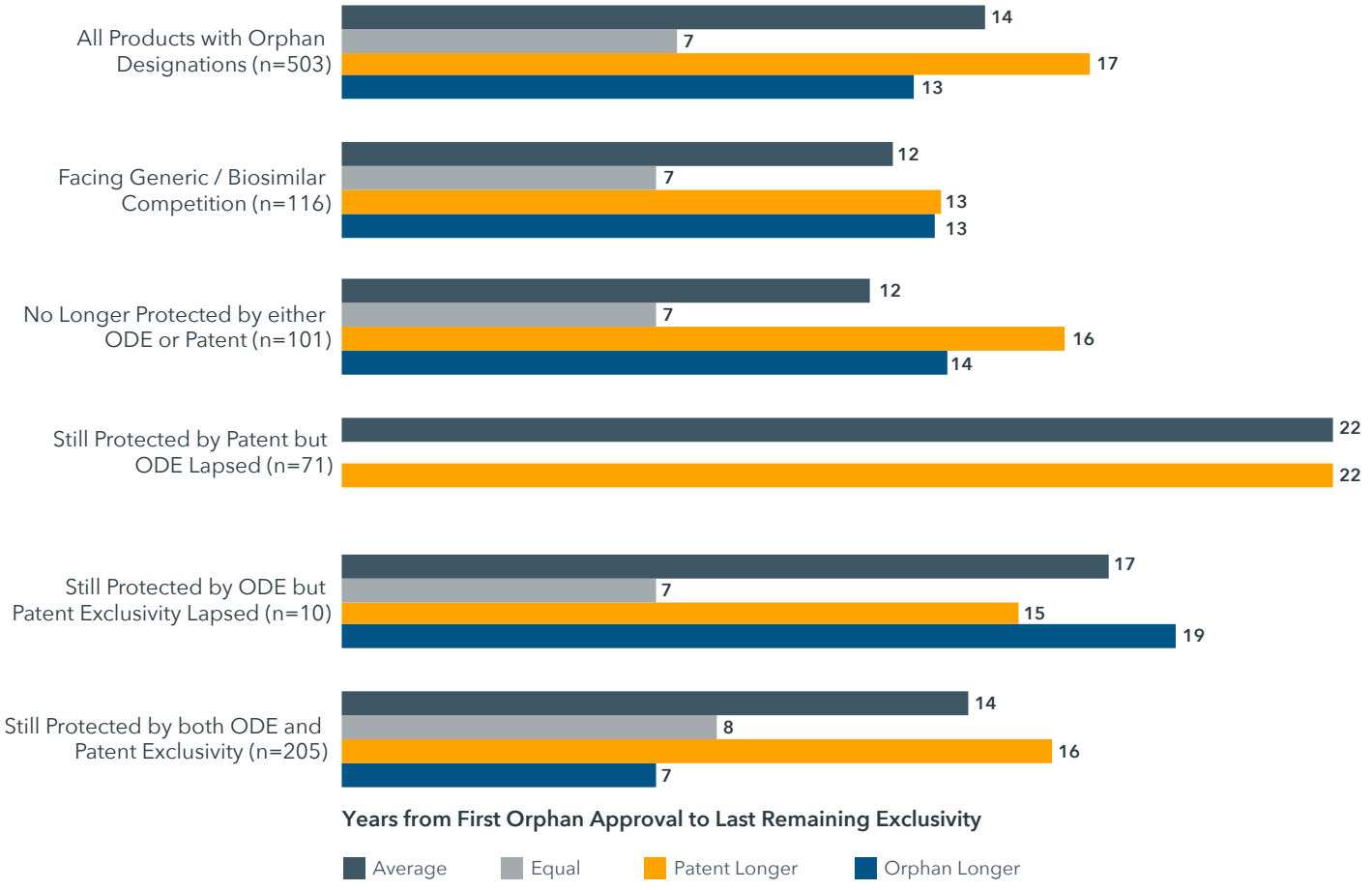
Source: FDA Orphan Drugs Database, FDA Orange Book, Accessed Sep 2018, IQVIA ARK Patent Intelligence, IQVIA National Sales Perspectives, Oct 2018; IQVIA Institute, Nov 2018

Notes: ODE = Orphan drug exclusivity; patent protection includes other forms of market exclusivity (e.g., pediatric extension, 505(b)(2)). Comparison of latest patent and earliest orphan exclusivity dates as the determination of longer duration.

ORPHAN AND PATENT EXCLUSIVITY FOR ORPHAN DRUGS

Orphan exclusivity only rarely extends beyond the exclusivity derived from patent protection to delay competitive entry, and when orphan exclusivity does extend later, it is typically due to a very short period of protection or other market exclusivity protections (see Exhibit 4). In some cases, development delays use up most of the 20-year patent duration, leaving only a few years of protection, or in other cases a 505(b)(2) application is granted exclusivity that is typically 3 or 5 years, but can be 7 years if it is also granted orphan status at launch. When orphan exclusivity does extend beyond the patent or other exclusivity, the exclusivity does not directly inhibit generics from competing in the other approved uses of a multi-indication drug. For some drugs with a mix of orphan and non-orphan indications where the orphan indication is granted late in the product's life, it does not necessarily delay generic entry for indications whose exclusivities have lapsed. Gleevec (imatinib), as an example, still has orphan exclusivity in effect until 2020 for pediatric Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL), however this did not delay generic entry in 2016 (upon patent expiry) for the eight other orphan indications all of which had lapsed by 2015.

Exhibit 4: Average Time from Orphan Designation to Final Exclusivity by Current Exclusivity Status



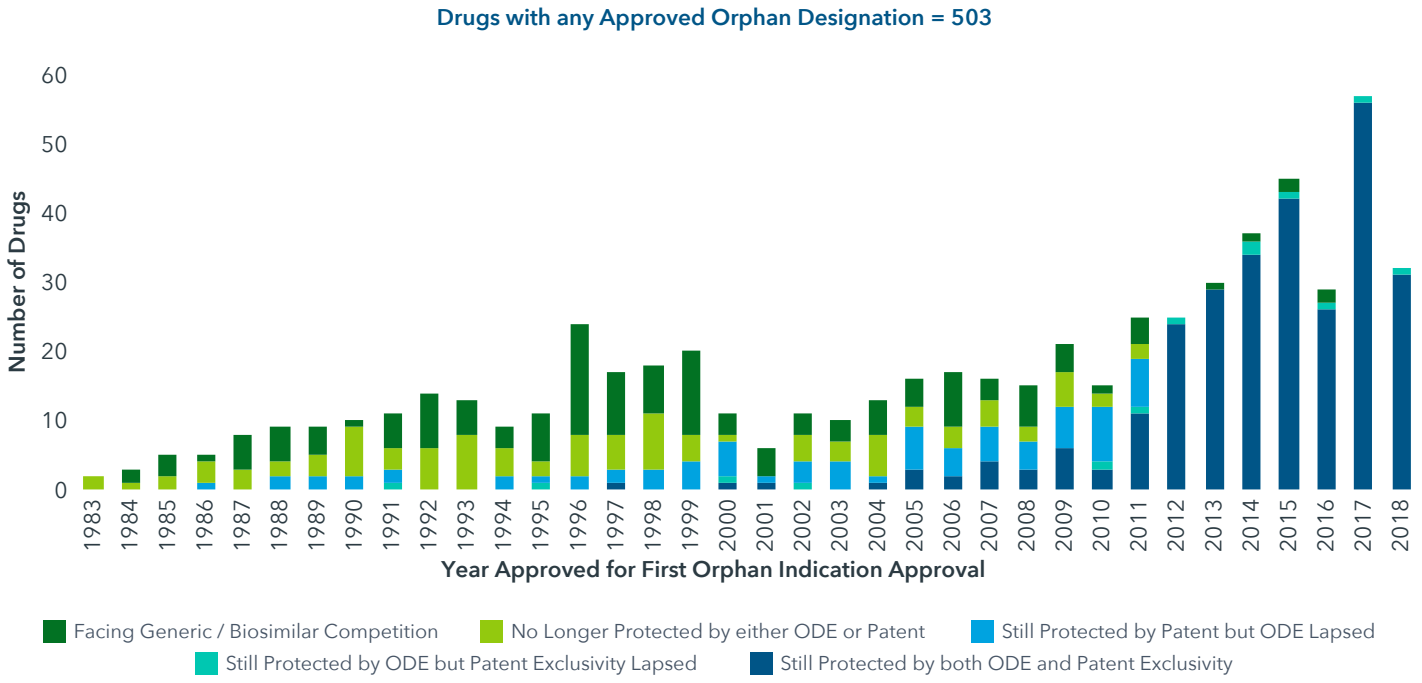
Source: FDA Orphan Drugs Database, FDA Orange Book, Accessed Sep 2018, IQVIA ARK Patent Intelligence, IQVIA National Sales Perspectives, Oct 2018; IQVIA Institute, Nov 2018

Notes: ODE = Orphan drug exclusivity; patent protection includes other forms of market exclusivity (e.g., pediatric extension, 505(b)(2)). Comparison of latest patent and earliest orphan exclusivity dates as the determination of longer duration.

ORPHAN AND PATENT EXCLUSIVITY FOR ORPHAN DRUGS

Most of the drugs with outstanding market exclusivity protection as of mid-2018 were first launched within the past 10 years (see Exhibit 5). There are some drugs where orphan exclusivity lapsed many years ago, but some form of patent protection is still active. These often include biologics or products with complex production processes. Still, some orphan drugs experience some level of market exclusivity for a period well in excess of seven years. These cases are often due to the drugs having been awarded multiple orphan designations that end at different times. Since orphan drug exclusivity (ODE) is indication-based rather than drug-based, the protection granted by orphan designation does not prevent generic competition on any non-orphan indications after patent expiry, nor on orphan indications where the exclusivity has expired.

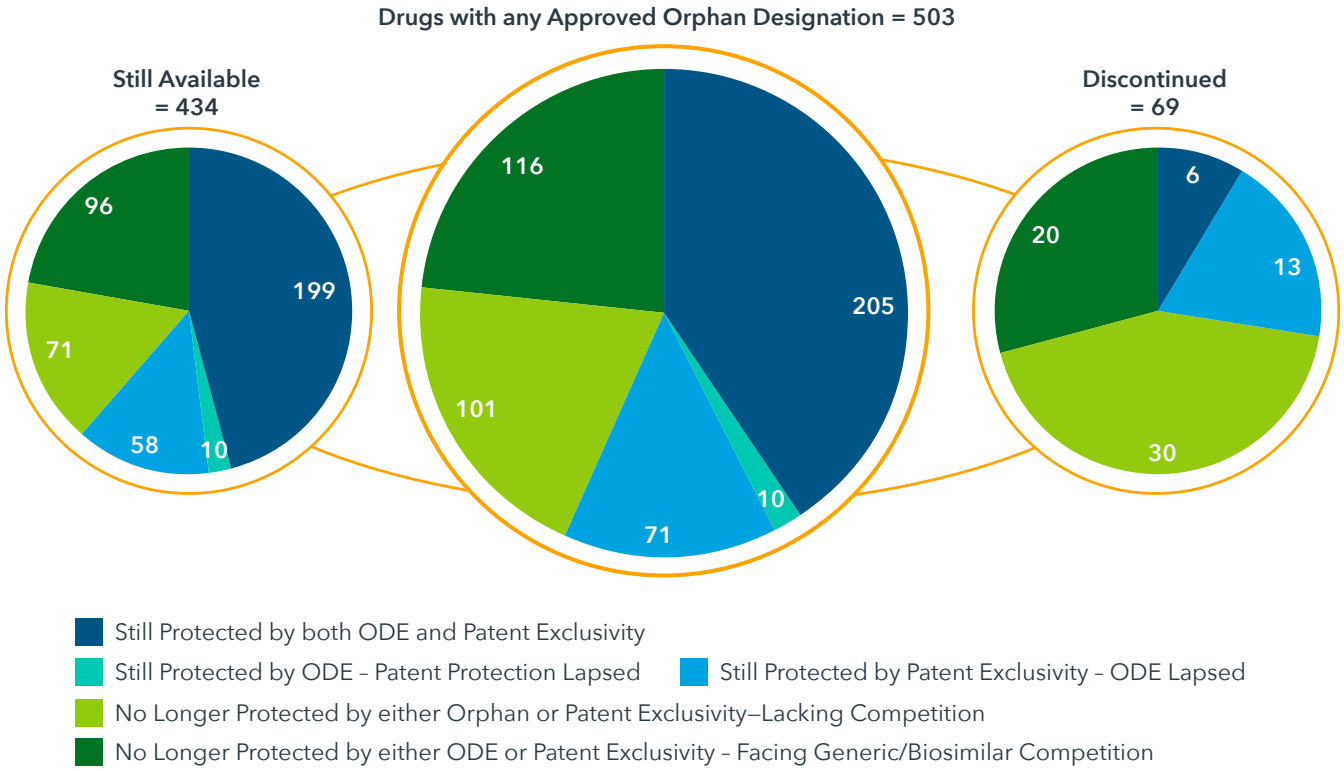
Exhibit 5: Orphan Designated Drugs by Current Exclusivity Status by Year of First Orphan Indication Approval



Source: FDA Orphan Drugs Database, FDA Orange Book, Accessed Sep 2018, IQVIA ARK Patent Intelligence, IQVIA National Sales Perspectives, Oct 2018; IQVIA Institute, Nov 2018

Notes: ODE = Orphan drug exclusivity; patent protection includes other forms of market exclusivity (e.g., pediatric extension, 505(b)(2)). Drugs with multiple orphan indications are assigned based on the first indication approval.

Exhibit 6: Orphan Designated Drugs with and without Patent Protection and Orphan Drug Exclusivity by Availability



Source: FDA Orphan Drugs Database, FDA Orange Book, Accessed Sep 2018, IQVIA ARK Patent Intelligence, IQVIA National Sales Perspectives, Oct 2018; IQVIA Institute, Nov 2018

Notes: ODE = Orphan drug exclusivity; patent protection includes other forms of market exclusivity (e.g., pediatric extension, 505(b)(2)).

Many of the orphan drugs whose exclusivity has lapsed but which are not yet facing competition reveal challenges that delay generic competition, such as small-revenue markets and reductions in their clinical use over time as new innovative products enter the market. Most are likely to remain the only treatment option available for that indication until a manufacturer ceases to produce them. For instance, 30% (n=30/101) of these have been discontinued by the manufacturer (see Exhibit 6). In total, there have been 69 discontinuations from the group of 503 orphan-designated drugs (14%), including another 20 that occurred after they faced generic competition and 19 while they were still protected. While the entrance of a competitor in a small-revenue market plausibly explains an originator's decision to discontinue manufacturing, the 49 decisions to exit without having faced competition imply that these medicines were not viable. They were either made less clinically relevant by subsequent innovations and some patients may have shifted to other treatments, or they were simply not profitable enough to continue. In those cases, discontinuation may be causing hardship for patients no longer able to access these treatments.

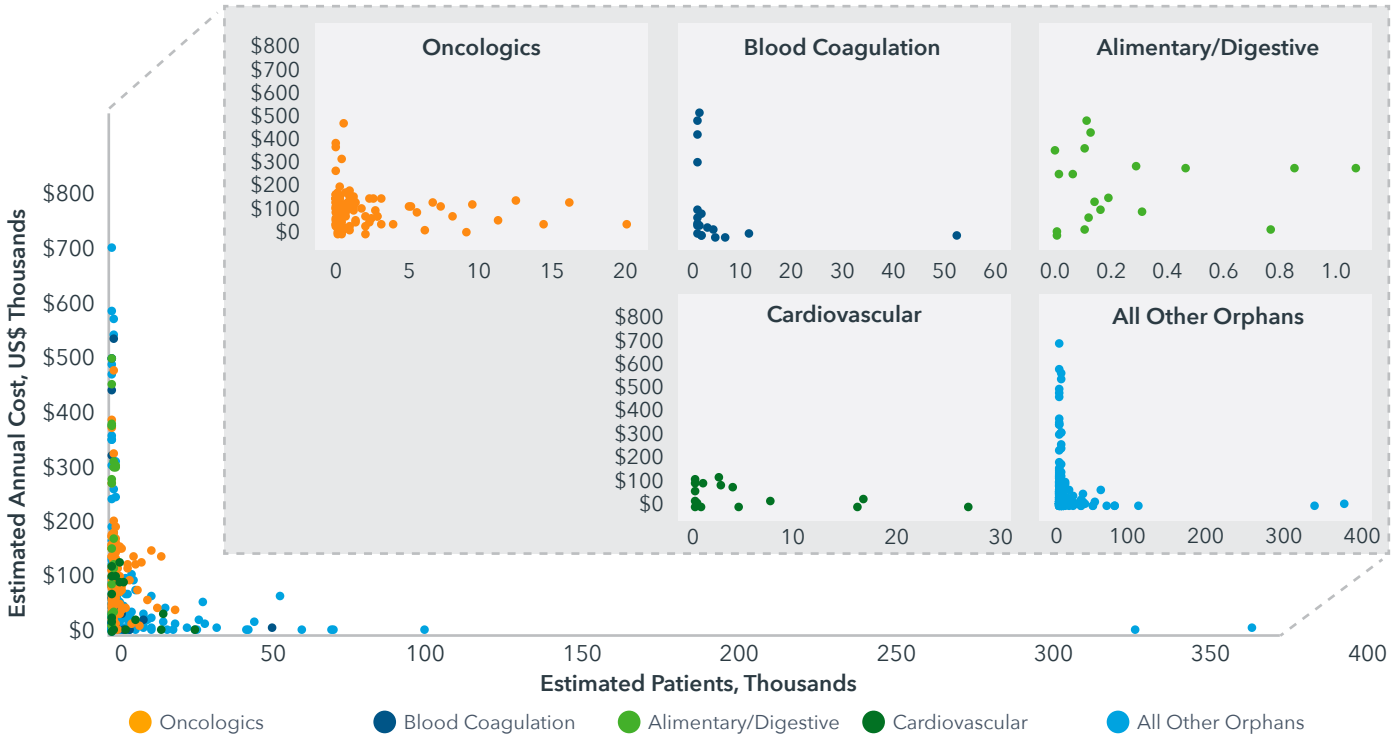
Pricing for orphan drugs

- Over the past five years, orphan drugs have exhibited an average price growth below the rate of the total branded market.
- On average, from 1993 to 2002, orphan drug price growth exceeded that of the overall branded market, but this growth dropped below the branded market in the 15-year period from 2003–2017.
- Orphan drugs have also demonstrated below-market price growth in the periods before and immediately after the granting of their first orphan designation.

In analyzing drug pricing it is important to include both the prices set at launch and how those prices evolve over time with annual or more frequent price increases (or decreases).

As noted in the Institute report *Orphan Drugs in the United States: Growth Trends in Rare Disease Treatments* (October 2018),[1] while some orphan drugs have prices exceeding $100,000 per year, the vast majority of those treat very few patients (see Exhibit 7). Although there are a notable number of recently-launched rare disease drugs that carry high prices, the aggregate spending on rare disease drugs has grown only modestly, from 4% of total market spending in 1997 to 10% in 2017.[1]

Exhibit 7: Estimated Target Patient Population Versus Cost for Orphan Drugs in the United States in 2017, US$ Thousands



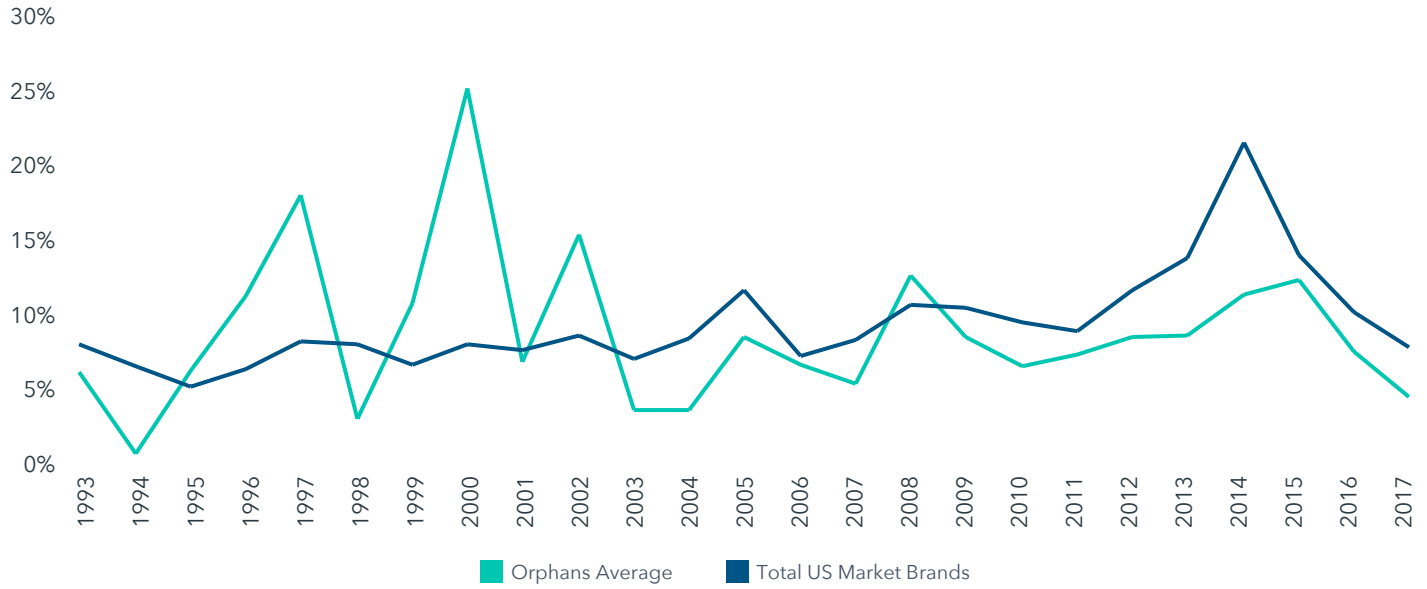
Source: IQVIA National Sales Perspectives, Jan 2018; FDA Orphan Drugs Database, accessed Sep 2018; IQVIA Institute, Sep 2018
Note: Though scales vary, all x-axes of charts within the zoom box display the number of patients in thousands.

PRICING FOR ORPHAN DRUGS

In looking at pricing trends over the past 25 years, price increases for orphan drugs have been slower than non-orphans for most of the last decade (see Exhibit 8), while they were higher than the market in the 1990's.

This is notable but perhaps not surprising as many orphan drugs approved in the 1990's were repurposed, older generic drugs, and the prices of these drugs were being reset to the new population.

Exhibit 8: Average Price Growth Per Year in the United States, Orphans versus Total Brand Market, 1993–2017

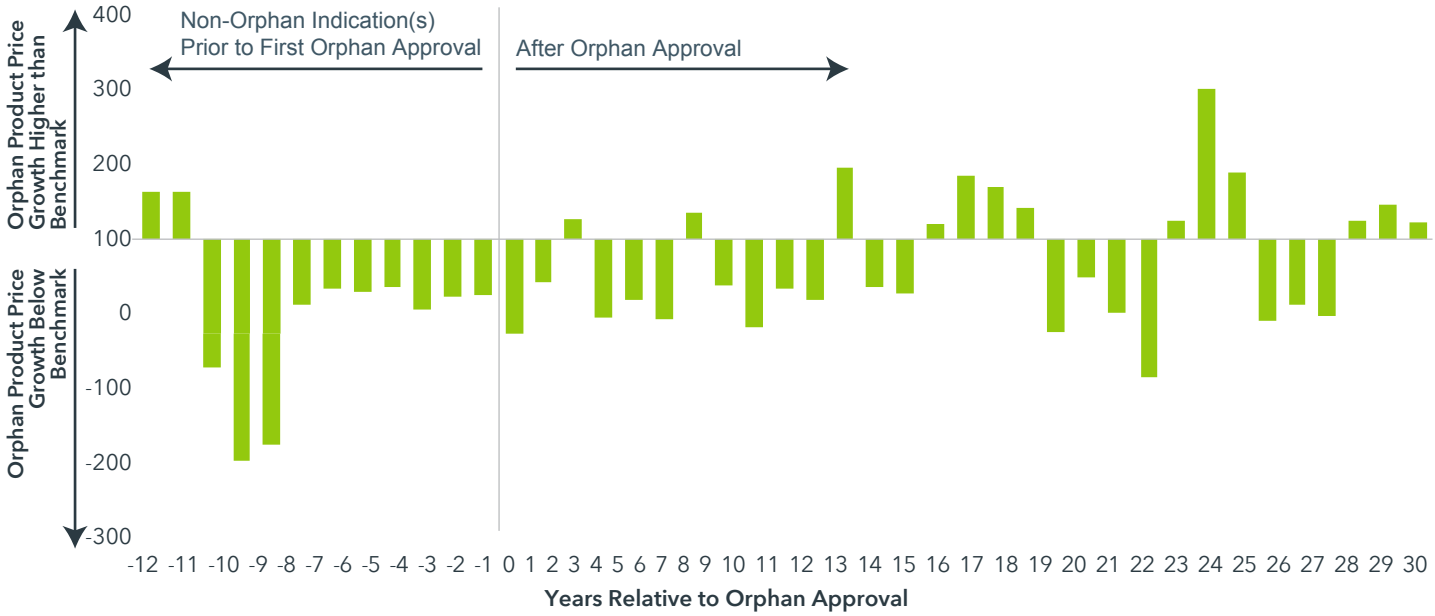


Source: FDA Orphan Drugs Database, FDA Orange Book, Accessed Sep 2018; IQVIA ARK Patent Intelligence, IQVIA National Sales Perspectives, Oct 2018; IQVIA Institute, Nov 2018

Drug pricing has varied in the overall market as well, while drugs which add an orphan designation (either at launch or after having been on the market for another use) have consistently raised prices more slowly than the market. By indexing drug price growth to the market average in specific time periods, and then time-aligning the indexed values to the time period when orphan status was added for a product, we see index values most often below the market average in that period (where the average = 100). This analysis enables the distinction between rising price increases in general in the past decade (see Exhibit 8) and whether the price increases for a product changed when it received an orphan designation (see Exhibit 9). By indexing price change to the benchmark in the relevant time-period, increases above the average show as an index value greater than 100, and those below average show as below 100. Negative index values reflect a price decline for the orphan drug. Overall, orphan drugs appear to have lower price increases in most years after their first orphan designation. The periods before orphan designation apply to those drugs which previously had non-orphan approved indications and shows that generally price increases were below the benchmark in the relevant year. In all, 10 of the 12 periods before orphan designation and 19 of the 31 periods after orphan designation had observed price increases below the benchmark rate. These periods include the years from 1993 to 2017, but as drugs were approved at different periods, not all periods have the same number of drugs. Outliers with either a low or a high index are generally due to limited numbers of products in that

period. In the periods 12 and 11 years prior to the first orphan designation, only three and four products were included respectively, and excluding the one product with very high price increases in that period, the indices would be 82 and 87. The product, in this case, was a blood factor VIII drug with a price per dose of $272 in 1995 which rose briefly to $363 in 1996 (11 years prior to orphan designation) and then declined to $1.32 by 2017. Similarly, for the periods 15 to 30 years after orphan designation, between 2–43 drugs are included in the index. In the periods closer to orphan designation, a greater number of records can be included, with an average of 24 drugs per period within the seven years prior to orphan designation, while there were 91 on average seven years after designation. These larger numbers of drugs still include some outliers in terms of large price increases or decreases but on average the group of drugs generally had lower price increases than the market overall.

Exhibit 9: Orphan Drug Price Growth Relative to Benchmark Price Growth, Time-Aligned to First Orphan Approval



Source: FDA Orphan Drugs Database, FDA Orange Book, Accessed Sep 2018, IQVIA ARK Patent Intelligence, IQVIA National Sales Perspectives, Oct 2018; IQVIA Institute, Nov 2018

Notes: Bars below the x-axis indicate that orphan pricing is below the benchmark/ brands of the time period. Bars above x-axis represent orphan pricing above benchmark/brands of the time period. The average of price growth index benchmark price growth in period = 100. Year 0 represents the first year post orphan designation.

Patient populations and treatment estimates for orphan drugs

- With few exceptions, orphan drugs are intended for very small populations, and the designations focus on those disorders with patient populations below 200,000 per year.
- Some orphan diseases are very well understood, readily diagnosed and more than half of the patients receive the indicated treatments, however, most rare diseases see much lower treatment rates.
- For rare diseases treatable by approved orphan drugs, an average of 10% of patients are receiving treatment with orphan drugs. Reasons for this low drug-treatment rate include undiagnosed patients and the availability of newer non-orphan therapies that supersede older, orphan drugs.
- About a quarter of orphan drug approvals target populations smaller than 5,000 patients, and for these diseases, treated patients average 13.5% of disease prevalence.
- Some orphan-designated medicines target diseases with populations greater than 200,000; these medicines were granted orphan status due to unlikelihood of financial returns, or in other cases, the disease epidemiology has changed or the clinical understanding has evolved.

The time it takes for a patient to be diagnosed and subsequently treated for a rare disease is often described by patient groups and advocates as "an odyssey". To quantify this odyssey, the following analysis has leveraged and compared estimates of treated patients for the specific rare condition, and the absolute number of patients for that condition (i.e., prevalence information, see Methodology).

NOTE ON RARE DISEASE ESTIMATES AND PRECISION

One of the key sources of epidemiology research, Orphanet,[2] provides helpful collation of incidence and prevalence estimates in summary before providing references to the specific research. Many of the diseases have a very wide range of prevalence estimates, but these typically fall in the range of 1–9 per 100,000. In the United States this translates to between 3,000 and 29,000 patients – a range that is ultimately not very precise. While the specific research referenced on the website is more precise than the above range, each study has its own approach to confidence and accuracy and are generally governed by academic standards and those of peer review journals. In this sense, the estimates are as accurate and reliable as research can make them today, and generally reinforce the idea that if estimating a patient population in theory is complex, identifying and treating them in the real-world must be equally challenging.

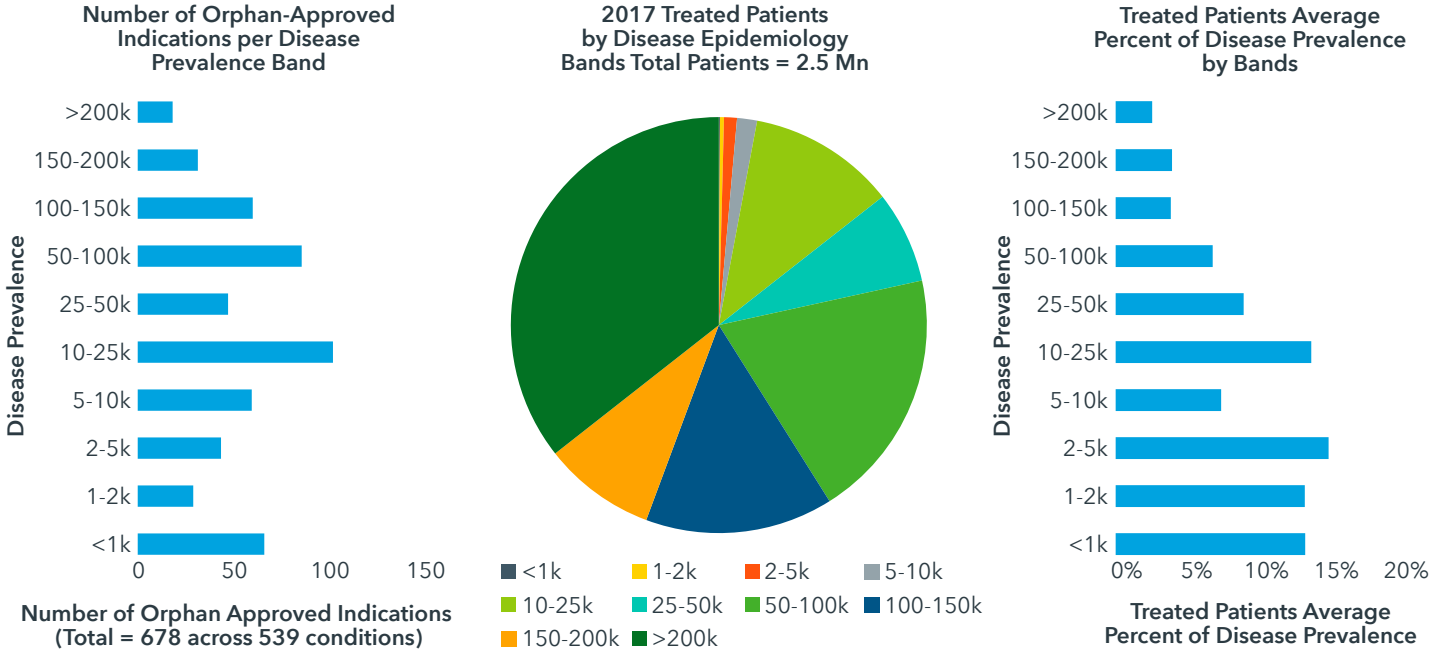
PATIENT POPULATIONS AND TREATMENT ESTIMATES FOR ORPHAN DRUGS

Approximately a quarter of approved orphan drug indications target populations smaller than 5,000 and treated patients for these indications average 13.5% of disease prevalence, suggesting that identification and diagnosis of these very rare diseases is challenging.

About 3% of diseases with an orphan designation have prevalence above 200,000. These were either granted through the exception for lack of financial returns or were cases where disease epidemiology has changed or where clinical understanding of the disease has evolved. For example, opioid dependence treatments were granted orphan status in the late 1990s and early 2000s, but the size of the opioid crisis in the United States far exceeds the 200,000-patient threshold. Rosacea was once thought to be rare but is now understood to affect nearly 16 million Americans.

Overall, the large-prevalence diseases with over 200,000 population that are the exception, relate to drugs that were used to treat 888,000 patients in 2017, about 36% of the 2.5 million total treated patients with orphan indications in 2017.

Exhibit 10: Orphan Disease Epidemiology and Treated Patients, United States, 2017



Source: FDA Orphan Drugs Database, Accessed Sep 2018, IQVIA National Sales Perspectives, Oct 2018; IQVIA Institute Nov 2018; Various public sources of epidemiological estimates (see Methodology)
Notes: Analysis includes 678 approved orphan designations across 539 distinct conditions reflecting that some conditions have multiple orphan designations.

On the other hand, diseases with very small populations present unique challenges to medical professionals to identify, diagnose, and treat, which is illustrated by how many indications have rates of treated patients between 0–5% of prevalence (see Exhibit 11).

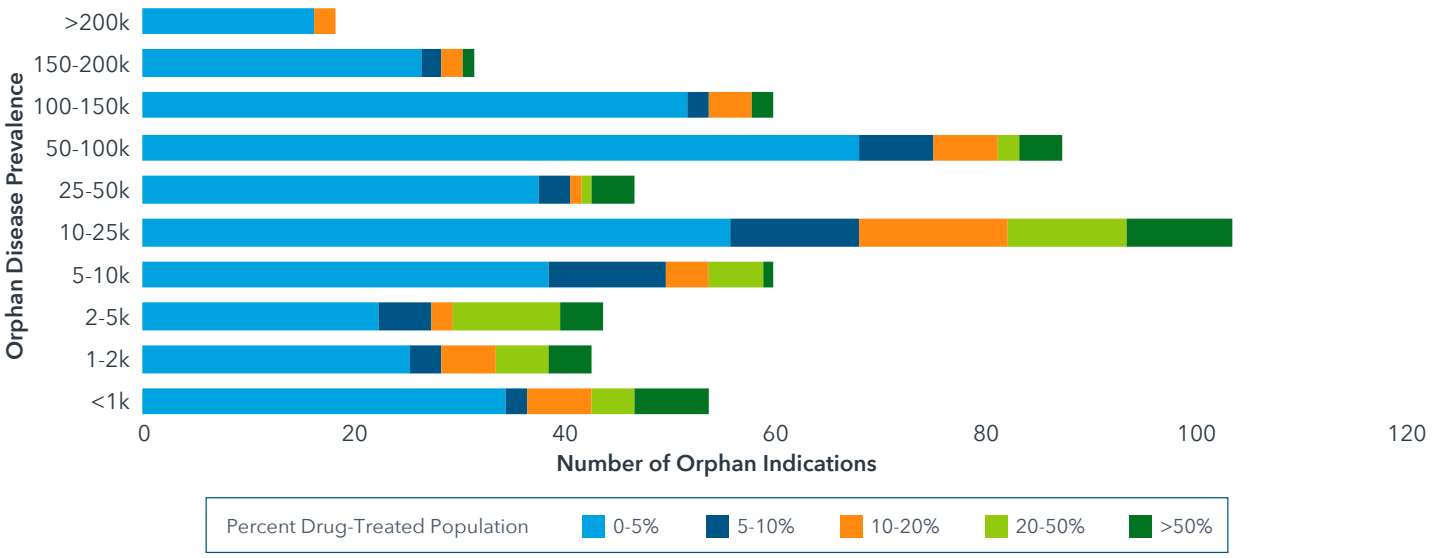
Treated patients across all rare diseases analyzed for this report average 10% of disease prevalence in a given year, as many remain undiagnosed or are otherwise ineligible for treatment. These percentages include all available orphan-designated therapies and in some cases include multiple generations of developed drugs. Still, even considering the fact that some older drugs may have fallen out of favor due to clinical advances, overall treatment rates remain extremely low. It is possible that patients are treated with the generic versions of some of the orphan drugs, or that they are treated with a subsequently approved medicine that did not receive orphan status, though these cases are uncommon.

In some cases, the prevalence estimated for the disease, such as pulmonary arterial hypertension, is very close to the annual treated patient counts, as they are clearly very symptomatic and well-characterized diseases

Other diseases, such as inherited genetic diseases or enzyme deficiencies, also often have very high rates of treatment, which is not surprising since they may be fatal without treatment. There are some orphan diseases, particularly infectious diseases, that are rare in the United States, and if the symptoms are mild they may never be brought to a doctor's attention, which was sometimes the basis for an orphan indication, where diagnosed incidence is only a small portion of much more common diseases (e.g., giardiasis).

The oft-described diagnostic odyssey is clearly an issue as relatively few patients are receiving treatment. Overall, improved diagnostic tools, disease awareness amongst healthcare providers, relevant clinical decision-making and active health-seeking behaviors by patients all contribute to the percentage of patients who ultimately receive treatment. These considerations do not include the potential for the influence of insurance coverage or patient's ability to cover healthcare costs which could be impacting treatment rates as well.

Exhibit 11: Number of Orphan Indications per Disease Prevalence Band and their Respective Percent Drug-Treated Population, 2017



Source: FDA Orphan Drugs Database, Accessed Sep 2018, IQVIA National Sales Perspectives, Oct 2018; IQVIA Institute Nov 2018; Various public sources of epidemiological estimates (see Methodology)

Notes on sources

THIS REPORT IS BASED ON THE IQVIA SERVICES DETAILED BELOW

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.

ARK Patent Intelligence™ is a database of biopharmaceutical patents or equivalents in over 130 countries and including over 3,000 molecules. Research covers approved patent extensions in 51 countries, and covers all types of patents including product, process, method of use and others.

Methodology

MARKET PROTECTION ANALYSIS

Manufacturers file and receive patents for their novel drugs early in the drug development process and these patents offer protection from competitors for 20 years once filed (subject to any additional extensions). In some cases, patent life may be nearing an end by the time the drug reaches the market. In addition to patent protection, the FDA can grant exclusive marketing rights to approved drugs thereby offering alternative or additional protection. Of note, any additional market exclusivity granted at the time of approval runs from the date of approval and is not added to the end of patent life, and so patents and exclusivity may or may not run concurrently. Thus, a drug may have an expired patent but receive market exclusivity at time of approval. These granted market exclusivities prevent the submission or approval of generic or biologics applications or 505(b)(2) applications with the goal to promote "a balance between new drug innovation and generic drug competition."[3] The length of time that the FDA grants a drug additional market exclusivity depends on the type of exclusivity. The following are abbreviated summaries of market exclusivities offered by the FDA relevant to the product that we studied:[3]

- New Chemical Exclusivity (NCE) or Biologic Exclusivity
  - Provides five years of market exclusivity for small molecules and 12 years for biologics
  - Runs from time of NDA approval or BLA first licensure
  - Prevents the FDA from accepting for review any other application for a drug containing the same active ingredient

- Orphan Drug Exclusivity (ODE)
  - Provides seven years of market exclusivity
  - Runs from time of NDA or BLA approval
  - Prevents the FDA from approving any other application for the same drug for the same orphan indication

- New Clinical Investigation Exclusivity
  - Provides for three years of market exclusivity
  - Runs from time of the new NDA approval
  - Granted to drug that was previously approved when an application or supplement reports new clinical investigations (e.g., new indication, new formulation)
  - Prevents the FDA from approving any other application for the same drug for a new indication or other new exclusivity

- Pediatric Exclusivity (PED)
  - Provides for six months added to the end of patents and/or exclusivity

- 180-Day Exclusivity
  - Provides 180 days of market exclusivity to the "first" generic applicant who challenges a listed patent by filing a paragraph IV certification and runs the risk of having to defend against a patent infringement suit

The market protection analysis examined the impact of the orphan drug exclusivity period and patent protection of orphan-designated therapies approved from 1983 through mid-2018, as well as the availability of generic competitors (small molecule or biologic) for therapies whose orphan drug exclusivity and patent protection had expired. Patents were identified via FDA's Orange Book and IQVIA's ARK Patent Database and additional market exclusivity time was calculated based on the types of exclusivities described above. Product patents are in general stronger than formulation or method of use patents,[4] and so when both existed, we used the protection provided by product patents in the analysis. Orphan drug designation can either be approved for new therapies or granted to already approved drugs. The market exclusivity protections for the latter category are

weaker due to the fact that generic manufacturers can enter the market for approved indications with lapsed exclusivity or patents while others remain protected (and thus are not an approved use for that generic drug). This scenario allows physicians to prescribe the generic drug on-label for some uses, but if they were to prescribe for the exclusive orphan indications it would dispensed as a brand unless the prescriber used a misleading diagnosis code linked to non-orphan uses.[3] To determine market protection in the case of multiple granted non-orphan exclusivities, the earliest expiration date was used. Generic and biologic drugs were identified using IQVIA National Sales Perspectives. For the purposes of analysis in this report, when there is discussion of patent protection versus orphan drug exclusivity, the patent protection in discussion includes the time of the patent protection plus any other form of exclusivity (e.g., pediatric exclusivity, etc.).

EPIDEMIOLOGY ESTIMATES

Methods to estimate the number of drug-treated patients and the number of patients with the orphan-approved indications are presented in the following sections.

For the analysis estimating drug-treated patients:

- The drug's label was reviewed to determine the aggregate dosing that would reach a typical patient in a year, with variations considered for chronic use, acute use and single use treatments
- Invoice price level costs were tracked using IQVIA National Sales Perspectives, and in combination with the dosing of the drug, were used to determine the cost of the drug per year
- Invoice level sales were divided by cost per year to determine the estimated number of patients
- Annual costs were validated against credible public statements from companies, advocacy groups or market observers referencing the annual costs, treated patients or cost per year for the drug
- Verification of company reported net sales was also undertaken to adjust IQVIA audited sales and better estimate patient populations where sales validation methods identified issues in IQVIA data capture

Orphan indication patient population was estimated using publicly available information including the following:

- Specific orphan-designated subpopulation prevalence was estimated from a credible peer-reviewed source, collated from relevant observational or regulatory bodies (e.g., the NIH's SEER program,[5] CDC[6]) or from rare disease patient groups (e.g., National Organization for Rare Disorders[7] or Orphanet[2]) which in turn often referenced peer-reviewed literature
- Combinations of patient subgroups were constructed by the IQVIA Institute based on public sources when a specific patient subpopulation noted in the orphan designation was not included in the publicly available literature
- Disease prevalence numbers in the United States were selected for analysis and in the absence of a publicly available U.S. prevalence, a global or developed market prevalence was used and the rate was adjusted to model the U.S. population
- Incidence was used for infectious diseases, diseases of newborns, acute/life-threatening conditions and others where duration of treatment was expected to be a year or less or where survival prognosis was deemed to be low. In these cases, the literature also did not include a prevalence estimate

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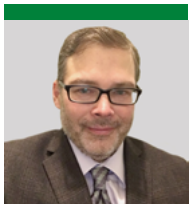
Murray Aitken is Executive Director, IQVIA Institute, which provides policy setters and decision-makers in the global health sector with objective insights into healthcare dynamics. He led the IQVIA Institute for Human Data Science (formerly the IMS Institute for Healthcare Informatics) since its inception 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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Michael Kleinrock serves as Research Director for the IQVIA Institute for Human Data Science, setting the research agenda for the Institute, leading the development of reports and projects focused on the current and future role of human data science in healthcare in the United States and globally. Michael leads the research development included in Institute reports published throughout the year. The research is focused on advancing the understanding of healthcare and the complex systems and markets around the world that deliver it. Throughout his tenure at IMS Health, which began in 1999, he has held roles in customer service, marketing, product management, and in 2006 joined the Market Insights team, which is now the IQVIA Institute for Human Data Science. He holds a BA degree in History and Political Science from the University of Essex, Colchester, U.K., and an MA in Journalism and Radio Production from Goldsmiths College, University of London, U.K.

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.

The IMS Institute is now the IQVIA™ INSTITUTE for Human Data Science

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