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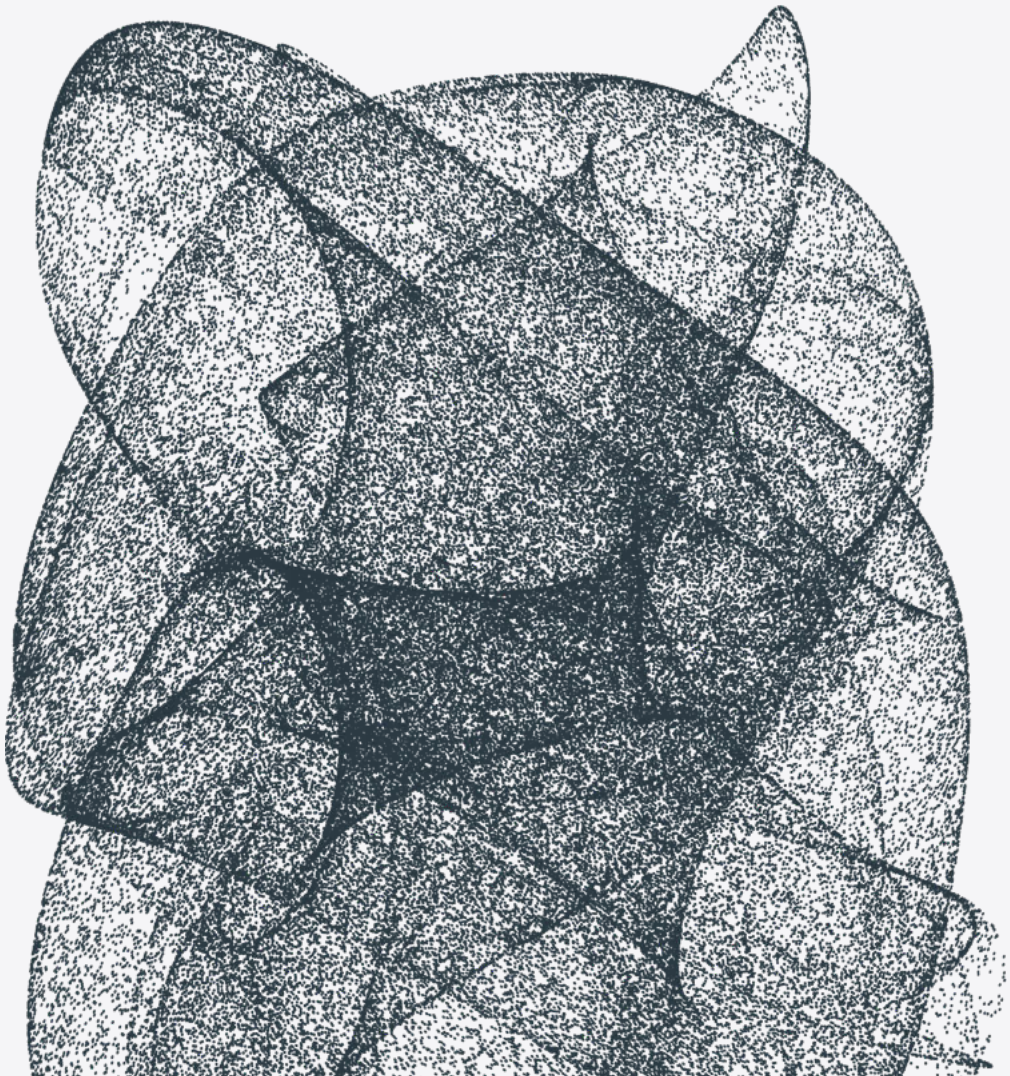
FOR HUMAN DATA SCIENCE

Orphan Drugs in the United States

RARE DISEASE INNOVATION AND COST TRENDS THROUGH 2019



DECEMBER
2020

Introduction

Rare disease drug approvals have accelerated significantly in recent years, with half of orphan indication approvals since the passage of the 1983 Orphan Drug Act (ODA) occurring in the past seven years. Even with these advances, patients continue to face challenges in receiving treatment, with most rare diseases lacking any approved treatments. Moreover, even when a treatment is available, it does not always reach the patients who would benefit from it.

This report examines trends in orphan drug approvals, the disease areas and patients they treat, and how these dynamics contribute to overall drug spending levels and growth. Transformative advancements have been made available to patients in 2019, highlighting the commitment made by manufacturers and regulators to patients. In the current COVID-19 pandemic, the challenges patients face in starting new treatments for rare diseases have been exacerbated by widespread health system disruptions, potentially delaying diagnosis and treatment of thousands of patients with rare diseases, ultimately risking worse disease outcomes.

This report continues a series of reports last updated two years ago, "Orphan Drugs in the United States: Growth Trends in Rare Disease Treatments," and brings important updates to key analyses tracked by stakeholders.

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 Barnard Gardocki, Onil Ghotkar, Deanna Nass, Alana Simorellis, Durgesh Soni and others at IQVIA are gratefully acknowledged.

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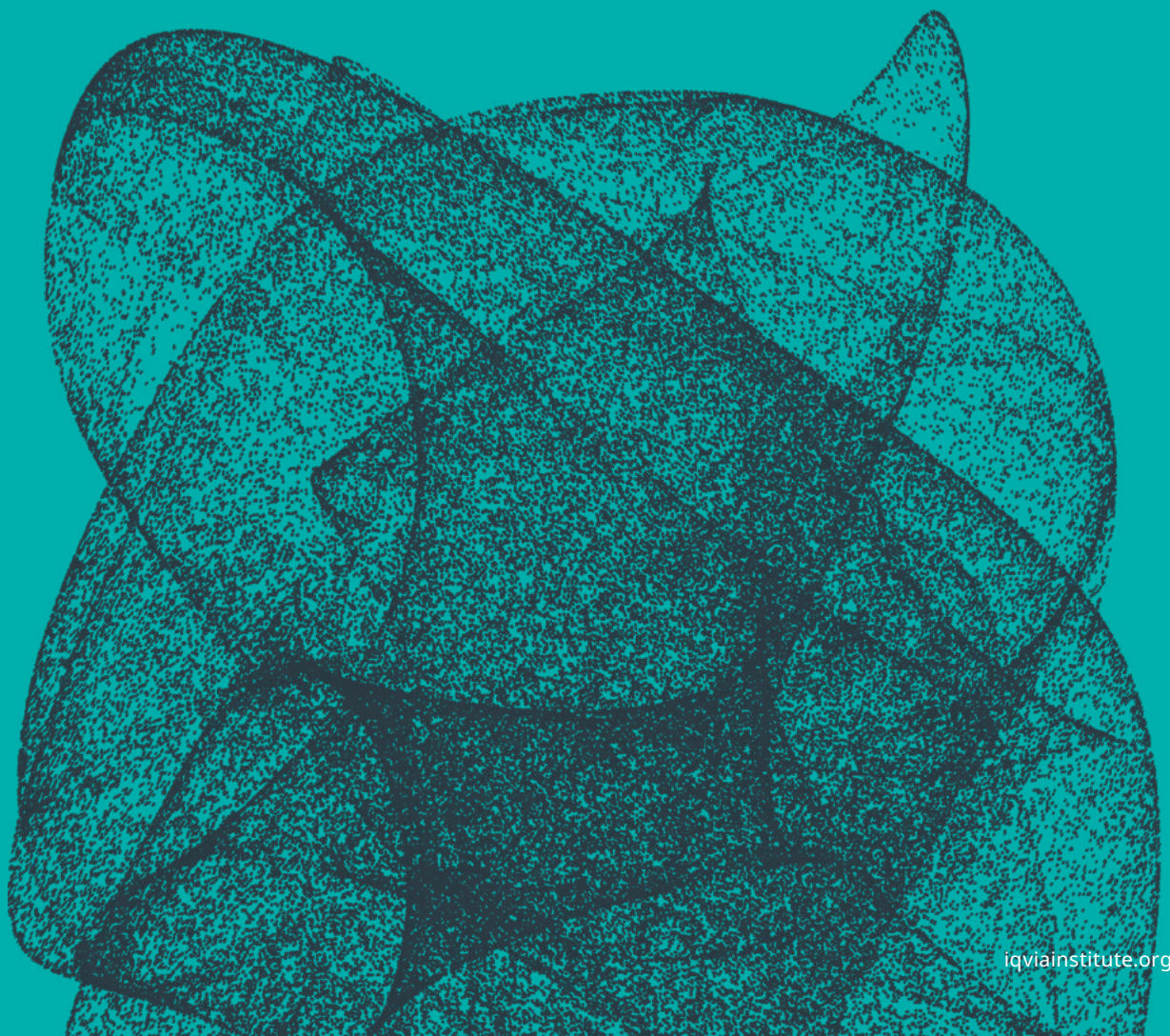


Definitions

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.

Biosimilar is a non-original biologic medicine produced through recombinant technology and approved through an abbreviated pathway, including the 351(k) pathway for biosimilars, 505(b)(2), and 351(a) pathways. The last two approaches occurred either prior to the implementation of the 351(k) pathway or because the manufacturer chose to submit their regulatory dossier via the alternative approach.

Defined Daily Dose (DDD) is the World Health Organization normalized measure of a day of therapy using standardized dosing assumptions. Note: this is unrelated to IQVIA's Drug Distribution Data offering, also named DDD.

Invoice 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 excludes off-invoice discounts and rebates that reduce net revenue received by manufacturers.

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 that do not meet the criteria for an orphan drug designation.

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.

Prevalence refers to the proportion of the population who have a specific disease within a given time period.

Specialty medicines are defined by IQVIA as those which treat Chronic, Complex or Rare diseases, **AND** which have a ***minimum of four*** out of seven additional characteristics related to the distribution, care delivery and/or cost of the medicines.

- Costly: => $6,000 USD/year
- Initiated/maintained by a specialist
- Requiring administration by another individual, or health care professional (i.e., not self-administered)
- Requiring special handling in the supply chain (e.g., refrigerated, frozen, chemo precautions, biohazard)
- Requiring patient payment assistance
- Distributed through non-traditional channels (e.g., 'specialty pharmacy')
- Medication has significant side-effects that require additional monitoring/counselling (including, but not limited to REMS programs) and/or disease requires additional monitoring of therapy (e.g., monitoring of blood/cell counts to assess effectiveness/side effects of therapy).

Traditional medicines are defined by IQVIA as all drugs that do not meet the criteria to be classified as a specialty medicine.

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.

Background

WHAT ARE RARE DISEASES?

- Rare diseases are serious, chronic illnesses that can become progressively disabling and can limit life expectancy.
- Although rare diseases are uncommon by definition, in aggregate the number of people with rare diseases is not insignificant: it is estimated that approximately 7% of the population in the developed world have a rare disease and the number is increasing.
- In the United States, the National Institutes of Health (NIH) estimates that between 25 million and 30 million people suffer from rare diseases – defined as those affecting fewer than 200,000 people.

CHARACTERISTICS OF RARE DISEASES AND THEIR TREATMENTS

- Rare disease patients and caregivers often shoulder a considerable burden for their disease and find it necessary to educate physicians about their condition and serve as their own advocates.
- Although there is increased awareness of rare diseases among healthcare stakeholders, patients often struggle to receive diagnosis and support; delays in diagnosis for rare diseases are common.
- A greater understanding of the biological pathways within rare diseases has allowed for development of novel therapies for patients eligible for treatment.

THE IMPACT OF THE ORPHAN DRUG ACT

- In the 1980s, rare disease patient advocacy groups formed a coalition that became the National Organization for Rare Disorders (NORD) and, along with Senator Orrin Hatch and with Representative Henry A. Waxman, were instrumental in passing the Orphan Drug Act in 1983, which provided incentives for drug manufacturers to develop therapies for rare diseases.
- The Orphan Drug Act has been universally considered a success. Orphan approved drugs and biologics are now available to treat rare diseases across numerous therapy areas and patient populations.

Key Elements of the Orphan Drug Act

Elements	Description	Impact
Rare disease definition	• < 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 provide incentives for drug manufacturers to provide treatment for rare diseases
Market exclusivity	• 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; for orphan drugs, the FDA will not award market authorization for a generic drug for the rare disease for seven years post-approval, a substantial incentive of superior patent protection
Tax incentives	• The Orphan Drug Tax Credit (ODTC) allows sponsors who have orphan designation to collect tax credit, which is 25% of applicable costs, for expenses occurred subsequent to issue of the designation for U.S. clinical trial costs on the orphan indication	The ODTC lowers the cost of drug development and is particularly beneficial to smaller manufacturers, who without the credit, may not be able to continue their development programs for treatments for rare diseases
Clinical research subsidies	• Orphan Product Grant program provides funding for clinical testing of new therapies to treat and/or diagnose rare diseases**	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 2,200, funded over 660 studies and helped 70 products gain marketing approval Receiving a grant from the Orphan Product Grant program eases the likelihood of marketing authorization
Other regulatory incentives	• 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.

Exhibit Notes: *Only three therapies have received orphan drug designation under this second definition for rare disease.

**Grants are modest and can run approximately $500,000/year.

Overview

INNOVATION IN RARE DISEASE TREATMENTS

- Significant and transformative innovations for patients with rare diseases have become available in 2019, including a gene therapy for children with spinal muscular atrophy and a cutting-edge nucleotide therapy for acute hepatic porphyria.
- In 2019, orphan indications have reached 838 in total since the passage of the Orphan Drug Act and have been granted to 564 distinct drugs, with an increasing number of drugs having multiple orphan indications.
- There are 343 drugs with approvals for a sole orphan indication, while 18 drugs have five or more orphan indications each.
- As there is significant unmet need in rare cancers, there has been a sustained increase in the number of new orphan indications in that space; 42% of the 491 orphan drugs approved over the past ten years have been for rare cancers.

ORPHAN INDICATION EXCLUSIVITY

- Biosimilars have made their way to the market even when there is remaining orphan exclusivity, as seen in oncology with bevacizumab (Avastin).
- It is not unexpected that biosimilars will be used for indications with ongoing protection for orphan indications. However, reimbursement dynamics in pharmacy benefit design may better enable market exclusivity for orphan indications. The expected first-time launches of adalimumab (Humira) biosimilars will be a test case for specialty pharmacy with ongoing orphan market exclusivity.
- Continued investment and commitment by manufacturers to pursue multiple orphan indications — as seen in cystic fibrosis — has led to increases in the patients eligible for treatment. As of 2019, 90% of cystic fibrosis patients are eligible for targeted treatment, compared to only 4% in 2012.

SPENDING AND COST TRENDS THROUGH 2019

- Invoice spending on drugs with orphan indications reached $58 billion in United States in 2019. This is 11% of total invoice spending in 2019 ($518 billion). Products with both orphan and non-orphan indications, for example adalimumab, accounted for $140 billion of invoice spending in 2019.
- Orphan drug costs are a concern. For example, orphan drugs have an average annual cost of $32,000, and more than a third of drugs with orphan indications cost more than $100,000 annually. However, high cost therapies are generally prescribed for a small portion of patients. Of the estimated 1.8 million patients treated in 2019 with an orphan-indicated drug, 77% used a drug with an annual cost less than $100,000.
- Since 2010, drug spending on orphan indications has risen from 6% to 11% of total invoice spending, and specialty medicines, which includes orphan and non-orphan drugs, increased from 25% to 47%. While both segments rose, this demonstrates specialty spending is not synonymous with orphan spending.
- Orphan invoice spending has been increasing at a rate of over 14% for the last five years, and faster than other specialty or traditional drugs for the past four, as vulnerable patients with high unmet need have been the focus of researchers, manufacturers, regulators, and patient advocacy groups.

COVID-19 IMPACT

- During the ongoing COVID-19 pandemic, new therapy starts (where a patient has not been on a treatment in the same therapy class in the last year) are down 21% for orphan diseases, suggesting new orphan disease diagnoses are not occurring.

A gene therapy for spinal muscular atrophy and an oral sickle cell treatment are among the novel transformative treatments in 2019

Exhibit 1: Notable Advancements in Treatments for Rare Diseases in the United States in 2019

NOVEL MEDICINE	ADVANCEMENT
Onasemnogene abeparvovec (Zolgensma) First gene therapy for children with spinal muscular atrophy (SMA)[1]	First gene therapy for any neurologic disease and potentially a one-time treatment for a leading genetic cause of infant mortality
Voxelotor (Oxbryta) First sickle cell treatment targeting the root cause of disease[2]	First-in-class once daily oral therapy which directly inhibits sickle hemoglobin polymerization
elexacaftor/tezacaftor/ivacaftor (Trikafta) First triple combination therapy for cystic fibrosis[3]	First triple combination therapy for the treatment of cystic fibrosis patients with a mutation found in 90% of patients
Caplacizumab (Cablivi) First nanotechnology treatment for acquired thrombotic thrombocytopenic purpura (aTTP)[4]	First in a new class of nanobody drugs, which utilize single-domain antibody fragments with unique structural and functional properties of heavy-chain antibodies
Givosiran (Givlaari) First precision genetic medicine advancement in the treatment of acute hepatic porphyria (AHP)[5]	The world's first approved RNA interference (RNAi) therapeutic
Fedratinib (Inrebic) First new treatment for myelofibrosis in a decade[6]	The first selective JAK2 kinase inhibitor for this disease; 50% of patients have mutations in the JAK2 gene
Triclabendazole (Egaten) First FDA-approved drug to treat fascioliasis[7]	Only drug approved by the FDA for fascioliasis, a neglected tropical disease, and is on the WHO essential medicines list

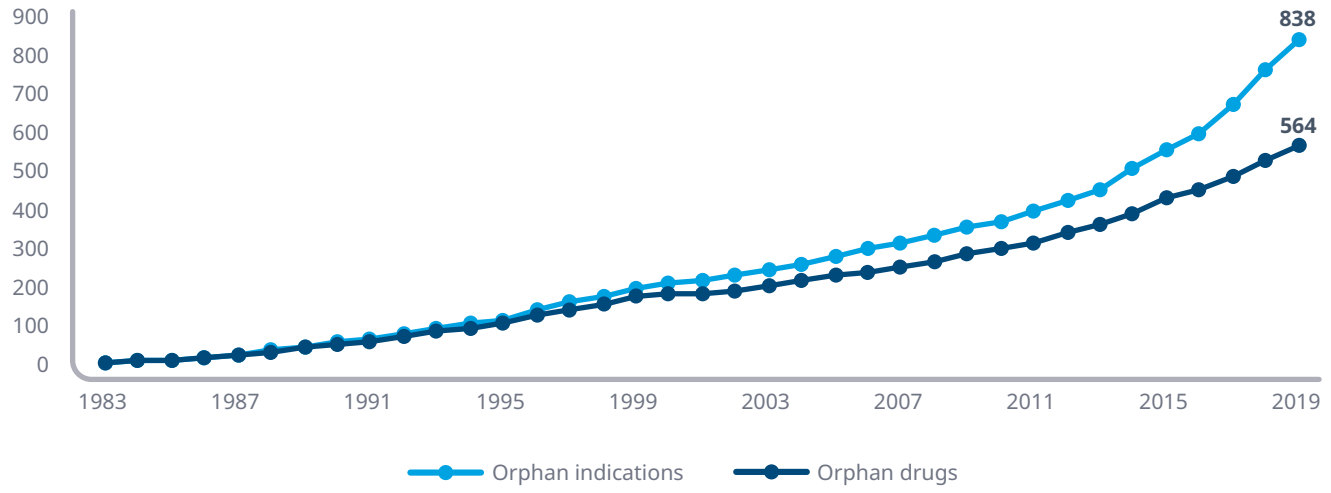
Source: IQVIA Institute Secondary Research, Aug 2020

- In 2019, there were significant advances in treatments for rare diseases, underscoring the commitment to patients by manufacturers and regulators.
- The first gene therapy for any neurologic disease, onasemnogene abeparvovec (Zolgensma), was approved for children under two years old with spinal muscular atrophy, which affects roughly 9,000 patients in the United States. The most severe form of the disease can be fatal in infants.
- Voxelotor (Oxbryta) is the only treatment available that addresses the root cause of sickle cell disease. For the estimated 100,000 patients affected, voxelotor mitigates the need for invasive procedures and potentially reduces pain medicine use in a vulnerable patient population.
- Elexacaftor/tezacaftor/ivacaftor (Trikafta) is now approved for patients with a F508 deletion on one allele of the CFTR gene, expanding the treatable patient population to 90% of cystic fibrosis patients (see Exhibit 8).
- Drugs with novel mechanisms of action, such as RNA interference (RNAi) and nanobody medicines —givosiran (Givlaari) and caplacizumab (Cablivi), respectively — were approved and reached the market.
- Fedratinib (Inrebic) was approved for myelofibrosis, a rare bone marrow cancer affecting ~5,000 people per year — the first approval in a decade for the disease.
- The first treatment for fascioliasis, a neglected tropical disease, was approved in the United States. It has been available in other countries since 2003.

Exhibit notes: All therapies listed were first marketed in 2019.

Total approved orphan indications since the passage of the Orphan Drug Act reached 838 by the end of 2019 and were awarded to 564 distinct drugs

Exhibit 2: Cumulative Number of Approved Orphan Indications and Distinct Drugs with at Least One Orphan Indication by Year of Marketing Approval



Source: IQVIA Institute, Aug 2020; FDA Orphan Drug Designations and Approvals[8]

- In 2019, the number of marketed drugs with an orphan indication reached 564, corresponding to 838 orphan indications.
- In the last three years, there have been 246 new orphan indications — approximately 30% of the total indications ever granted under the Orphan Drug Act (ODA).
- In addition to novel therapies initially receiving orphan designation, many products receive orphan designation after launch. Specifically, 76 novel drugs had orphan designation at launch in the past three years, while there were 116 orphan indications approved total in the same period.
- The number of approved orphan indications is growing faster than the number of drugs because some drugs have multiple indications. In 2019, 25% of drugs have more than one orphan indication.
- Multiple orphan indications for the same medicine are increasingly common, particularly in cancer and autoimmune diseases, where research has revealed targeting a single pathway can have an impact on several similar diseases (see Exhibit 3 for more detail).

Exhibit Notes: Chart displays designated and marketing-approved indications by marketing approval date. Distinct drugs are plotted based on year of marketing approval of first orphan designation.

There are 343 drugs with approvals for a sole orphan indication, while 18 drugs have approval for five or more orphan indications

Exhibit 3: Drugs With Any Orphan Approval by Their Number of Orphan Indications and Whether They Also Have Non-Orphan Indications

Number of Orphan Indications	Orphan-Only Indication Drugs	Orphan and Non-Orphan Indication Drugs	Total Drugs
1	343	79	**422**
2	73	17	**90**
3	17	10	**27**
4	5	2	**7**
5+	9	9	**18**
Totals	**447**	**117**	**564**

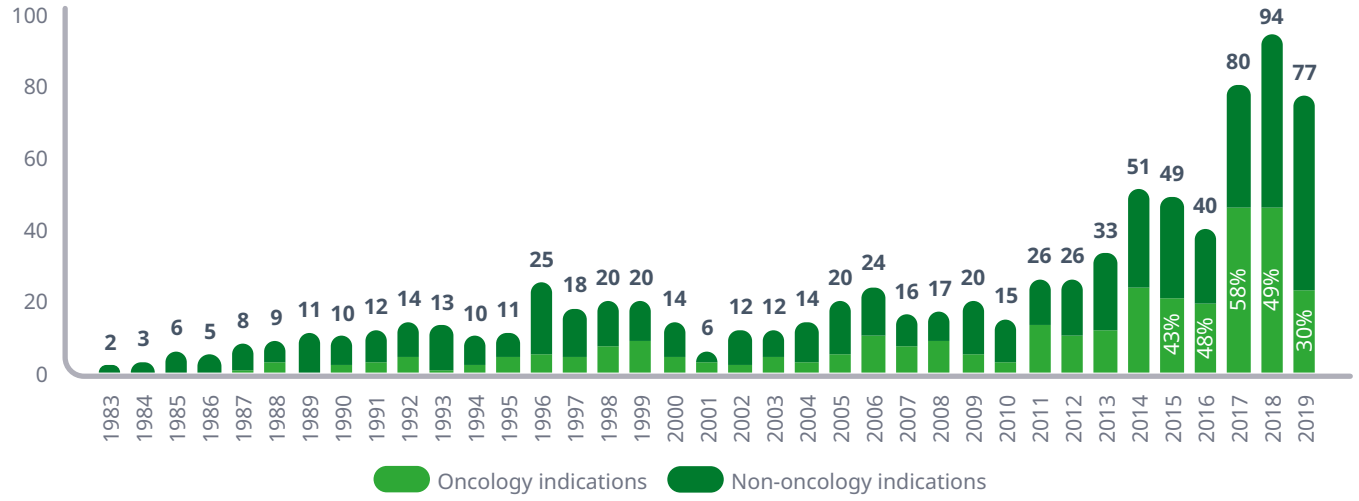
Source: IQVIA Institute, Aug 2020; FDA Orphan Drug Designations and Approvals[8]

- The majority of drugs with orphan indications treat only one rare disorder, specifically, 343 out of 564 drugs with orphan approvals have a singular orphan indication.
- Overall, there are 447 drugs with orphan-only indications, with 104 drugs approved for two or more orphan indications.
- A drug can have both orphan and non-orphan indications. There are 79 drugs that have non-orphan indications and a single orphan designation, bringing the total number of drugs with a single orphan indication to 422.
- Excluding these, the remaining 142 drugs each have two or more orphan indications, and account for 416 indications between them.
- Orphan drugs with multiple indications are most often therapies for rare cancers, where 63 drugs have two or more orphan indications. The second most common therapy area for multi-orphan indication drugs is blood disorders, where there are 11 drugs.
- Of the 18 drugs with more than five orphan indications, 12 are treatments for rare cancers and the remaining drugs treat autoimmune diseases, other immune system defect diseases, metabolic disorders, and blood disorders.

Exhibit Notes: Table only includes drugs with approved and marketed orphan indications.

The significant increase in new orphan indications has been focused in rare cancer treatments, which account for 45% of approvals since 2015

Exhibit 4: Number of Oncology Versus Non-Oncology Orphan Indication Approvals in the U.S. 1983–2019



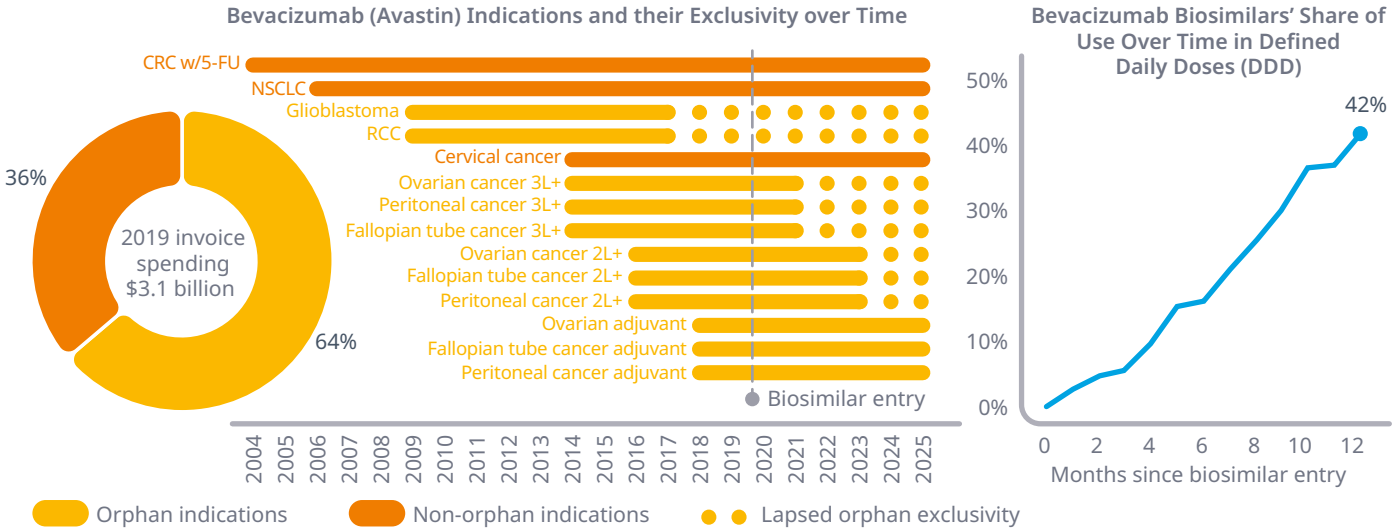
Source: IQVIA Institute, Aug 2020; FDA Orphan Drug Designations and Approvals[8]

- In the 37 years since the passage of the ODA, 838 indications have been granted orphan status, which confers seven years of exclusivity along with other incentives (see Overview).
- Rare cancers have been a focus for manufacturers seeking orphan indications, comprising 42% of approved orphan indications from 2010–2019. This is an increase from the 34% of orphan indications approved from 2000–2009.
- Of all orphan designated drugs receiving marketing approval, half have been approved since 2013, as a significant bolus of new rare disease treatments have reached the market.
- In this time frame, the average number of orphan indications receiving marketing approval per year has reached 67 — a notable increase from the average of 21 per year seen prior to 2013.
- While year-to-year variations are common, the increase in the last three years is noteworthy, with 251 designations representing 30% of all approved orphan indications since 1983.
- While orphan exclusivity confers market exclusivity for the seven year period, it has not necessarily extended the protected life for a product, as drugs patents often extend past the period of orphan exclusivity.[9]

Exhibit Notes: Displays designated and marketing approved indications by marketing approval date. FDA granted designations are not counted until marketing authorization has been approved. Oncology definition aligns with NIH rare cancer definition.

Bevacizumab biosimilars have launched and are being used across all indications, including those with orphan exclusivity

Exhibit 5: Current Bevacizumab Invoice Spending, Exclusivity by Indication, and Biosimilar Use



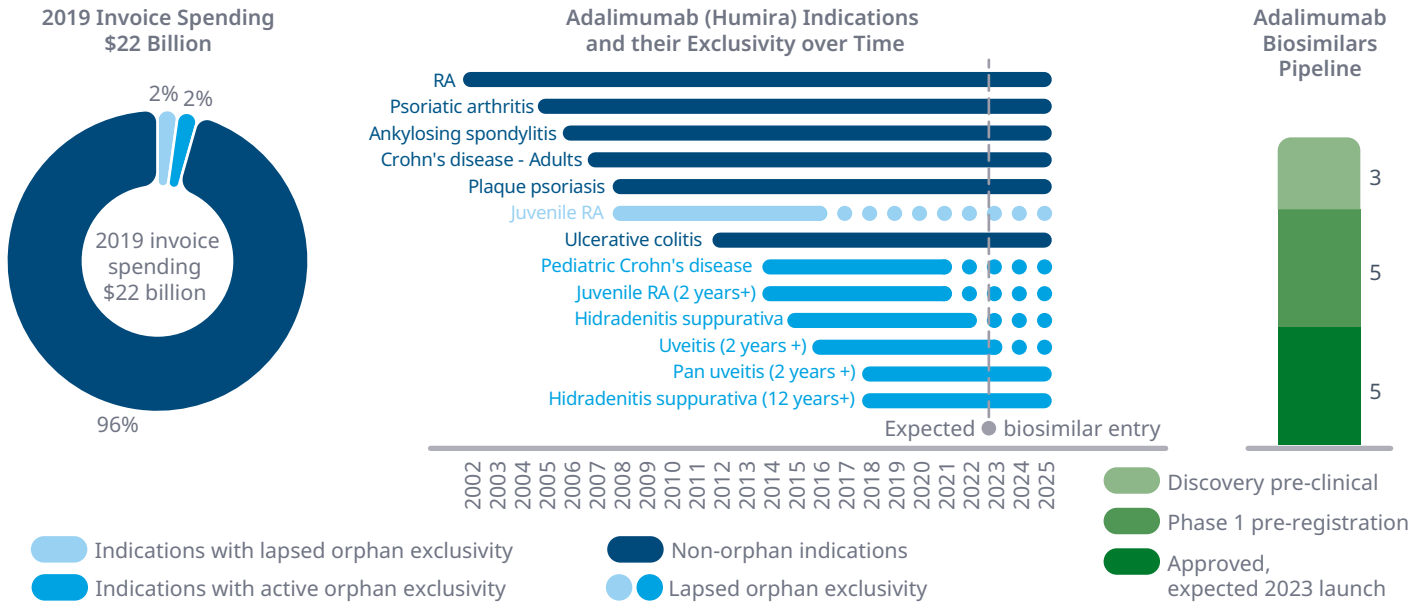
Source: IQVIA Institute, Aug 2020; FDA Orphan Drug Designations and Approvals;[8] IQVIA National Sales Perspective, Jan 2020

- Bevacizumab (Avastin) is currently approved for three non-orphan and 11 orphan indications. In 2019, 64% of its $3.1 billion sales were due to orphan indications, while the remaining 36% were generated from non-orphan indications.
- Of its 11 approved orphan indications, nine were still under orphan exclusivity when the first bevacizumab biosimilar product launched in July 2019. These indications are centered around treating ovarian, peritoneal, and fallopian tube cancer at various points in the treatment paradigm.
- Biosimilar bevacizumab products have reached 42% of volume share in their first full year on the market, and are expected to reach approximately 60% by the end of the first two years on the market.[10]
- Some providers that see a high number of patients, including those with rare diseases, use only biosimilar products in their practice,[10] suggesting that they are using biosimilars for orphan diseases despite remaining market exclusivity for those indications.
- Additionally, the presence of claims data for these diagnoses show biosimilar bevacizumab is being used for orphan-exclusive indications (data not shown).
- Similarly, small molecule generics have reached the market prior to orphan exclusivity lapses.[11] Taken together, these findings suggest biosimilar bevacizumab is being used to treat orphan indications with remaining market exclusivity.

Exhibit Notes: See Definitions page for IQVIA Institute definition of Defined Daily Dose (DDD). Bevacizumab biosimilars launched in July 2019.

Adalimumab sales totaled $22 billion at invoice prices in 2019, with 4% from orphan indications, and biosimilars are expected in 2023

Exhibit 6: Current Adalimumab Invoice Spending, Exclusivity by Indication, and Biosimilars Pipeline



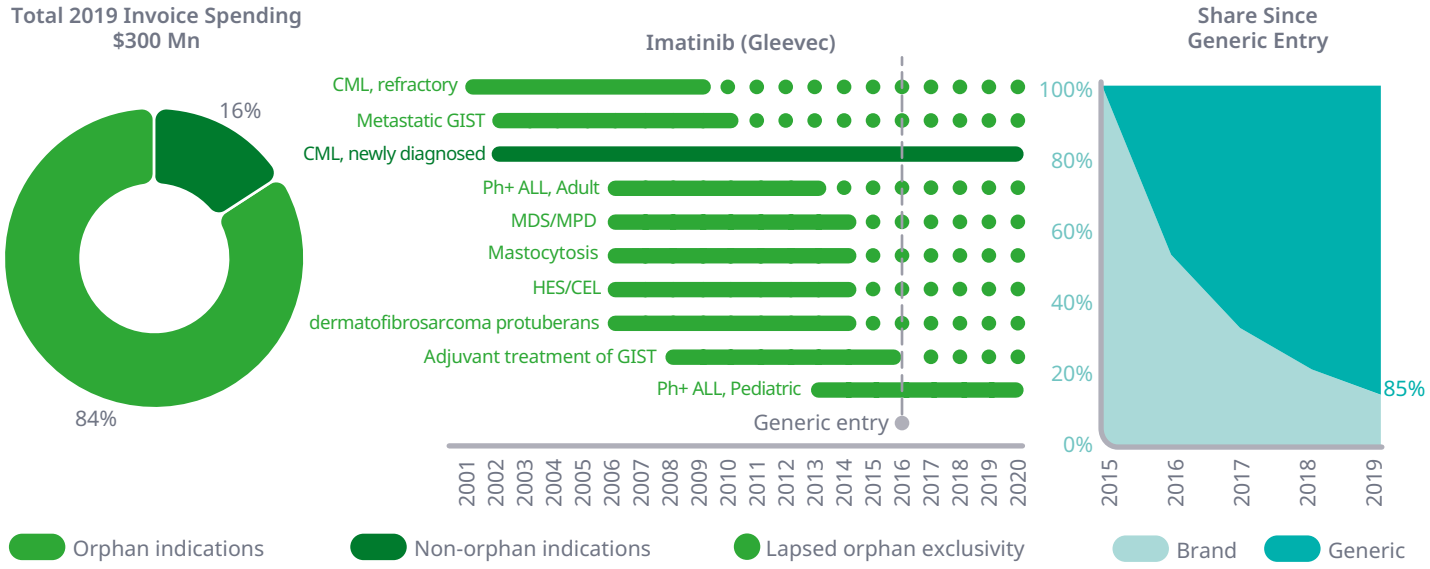
Source: IQVIA Institute, Aug 2020; FDA Orphan Drug Designations and Approvals;[8] IQVIA National Sales Perspective, Jan 2020

- Adalimumab (Humira) currently has 13 indications approved, six non-orphan and seven orphan indications. The orphan indications account for 4% of invoice spending in 2019, 2% of which is from the orphan juvenile rheumatoid arthritis indication, which no longer confers orphan exclusivity.
- The remaining six orphan indications comprise the other 2% of sales, and orphan exclusivity in these indications remains active, with the last expiring in 2025.
- Settlements between biosimilar manufacturers and the originator manufacturer will allow the first biosimilar launches in January 2023, though orphan exclusivity for pan uveitis in patients at least two years old and hidradenitis suppurativa in patients as young as 12 years old are expected to extend to 2025.
- However, biosimilar approvals will be limited to lapsed orphan indications. Nonetheless, as seen in bevacizumab biosimilars, it is expected that the use of biosimilar adalimumab will occur across all indications.
- It is not unexpected that biosimilars will be used for indications with ongoing protection for orphan indications. However, reimbursement dynamics in pharmacy benefit design may better enable market exclusivity for orphan indications. The expected first-time launches of adalimumab (Humira) biosimilars will be a test case for specialty pharmacy with ongoing orphan market exclusivity.

Exhibit Notes: Adalimumab biosimilars are expected to launch in Jan 2023 based on litigation settlement agreements.

Imatinib generics launched while orphan exclusivity for Ph+ ALL was still in place and rapidly gained 85% of volume share

Exhibit 7: Current Imatinib Invoice Spending, Exclusivity by Indication, and Generic Use



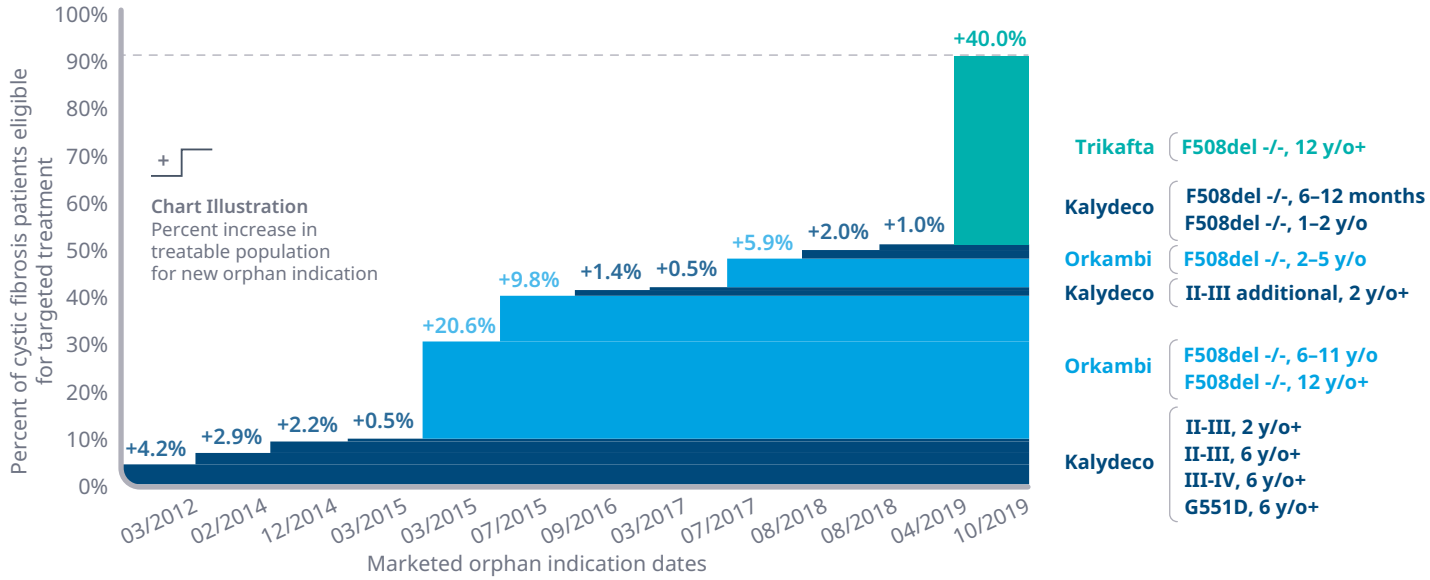
Source: IQVIA Institute, Aug 2020; FDA Orphan Drug Designations and Approvals[8]; IQVIA National Sales Perspective, Jan 2020

- Imatinib (Gleevec) is currently approved for one non-orphan and nine orphan indications. In 2019, 84% of its $300 million sales were due to orphan indications, while the remaining 16% were generated from the non-orphan indication.
- Of the orphan indications, only one had market exclusivity for the orphan indication when the first imatinib generic product launched in February 2016. The protected orphan indication is for the treatment of Philadelphia chromosome-positive acute lymphocytic leukemia (Ph+ ALL) in pediatric patients.
- In total, generic imatinib products have reached 85% volume share from their initial launch to 2019 and reached nearly 70% of generic volume share after only two years on the market.
- Imatinib is not the only product to face generic entrants prior to orphan exclusivity lapses.[11] However, it is unclear at this time if generic imatinib products are being used to treat Ph+ ALL pediatric patients, which is still protected.
- The availability of generics and the resulting pricing pressure from their entry into the market highlights how some investments made by manufacturers to reach additional patient populations may generate less financial return and underscores the market complexities of multi-indication drugs.

Exhibit Notes: CML = chronic myeloid leukemia; GIST = gastrointestinal stromal tumor; Ph+ ALL = Philadelphia chromosome-positive acute lymphocytic leukemia; MDS = myelodysplastic syndrome; MPD = myeloproliferative disorder; HES = hypereosinophilic syndrome; CEL = chronic eosinophilic leukemia.

Continued investment in cystic fibrosis has expanded the treatable patient population to 90% of estimated prevalence

Exhibit 8: Timeline of Cystic Fibrosis Orphan Indications and Share of Eligible Treatment Population, 2012–2019

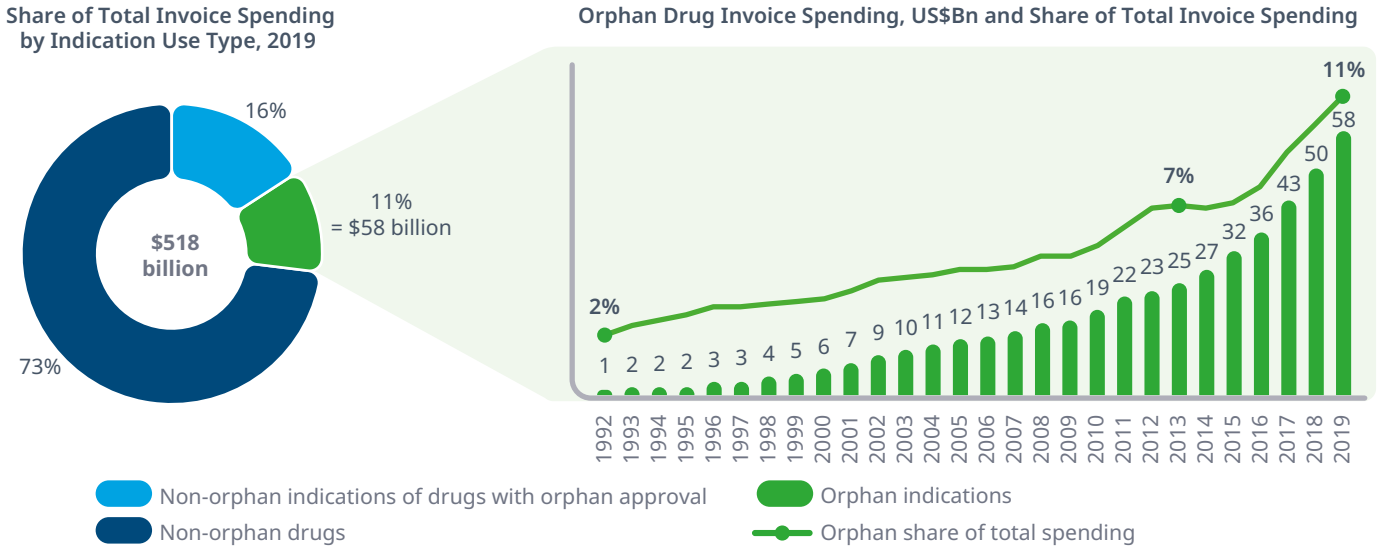


Source: IQVIA Institute, Aug 2020; FDA Orphan Drug Designations and Approvals[8]

- Continued investment by manufacturers in orphan indications has brought critical treatments to underserved patients in a relatively short amount of time, as seen in the cystic fibrosis patient population.
- In 2012, ivacaftor (Kalydeco) received its first orphan indication for patients with a G551D mutation in the CFTR gene, found in approximately 4% of patients.
- Within the next two years, ivacaftor received two additional orphan indications, one for each the II-III and III-IV classes of CFTR mutations,[11] meaning approximately 23% of the cystic fibrosis patient population was eligible for treatment with this drug.
- In the following years, theratyping data was accepted by the FDA for additional approvals to expand the treatable patient population. Theratyping is the process of determining a patient's response to drugs *in vitro*. The approvals of ivacaftor/lumacaftor (Orkambi), ivacaftor/tezecaftor (Symdeko), and additional ivacaftor indications increased the treatable patient population to 40% of disease prevalence.
- Additionally, ivacaftor received another orphan indication based on mutation, wherein patients with a F508 deletion on both alleles of the CFTR gene (homozygous), were eligible for treatment.
- In 2019, only seven years after ivacaftor's initial approval, elexacaftor/tezacaftor/ivacaftor (Trikafta) was approved for patients heterozygous for the F508 deletion, meaning it occurs on only one allele, and has expanded the treatable patient population to 90% of prevalence.

Orphan indication invoice spending accounts for 11% of United States' invoice spending, totaling $58 billion in 2019

Exhibit 9: Invoice Spending on Orphan Drugs in the United States 1992–2019, US$Bn

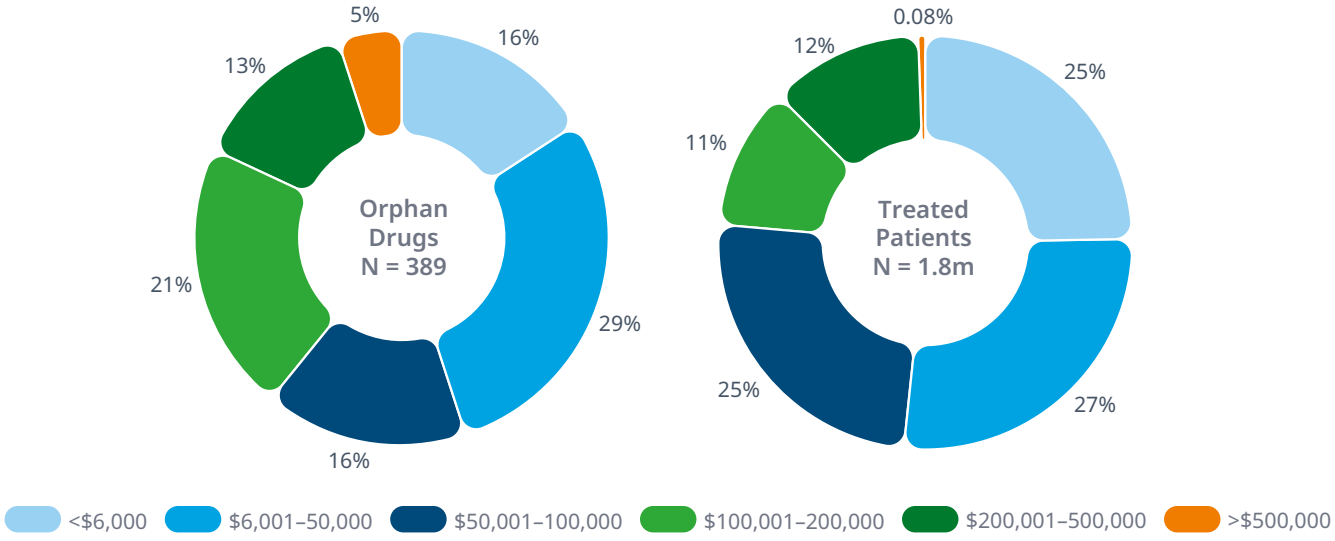


Source: IQVIA Institute, Aug 2020; FDA Orphan Drug Designations and Approvals;[8] IQVIA National Sales Perspective, Jan 2020

- The total invoice spending on orphan indications accounted for 11%, or $58 billion of total invoice spending in 2019, while $378 billion was spent on non-orphan drugs.
- The remaining 16% of invoice spending, or $82 billion, was spent on the non-orphan indications of drugs that have both orphan and non-orphan indications.
- The significant increase in the numbers of orphan approvals has raised orphan share of invoice spending from 2% in 1992 to 11% in 2019, and up from 7% of invoice spending in 2013.
- While many drugs with significant total invoice spending also have orphan designations, it is rare for the orphan uses to account for more than a fraction of total spending.

In 2019, 39% of orphan drugs cost more than $100,000 annually, but they are used to treat only 23% of patients with rare diseases

Exhibit10: Orphan Drugs and Patients Treated by Drugs with an Orphan Indication in 2019 by Annual Drug Cost Bands



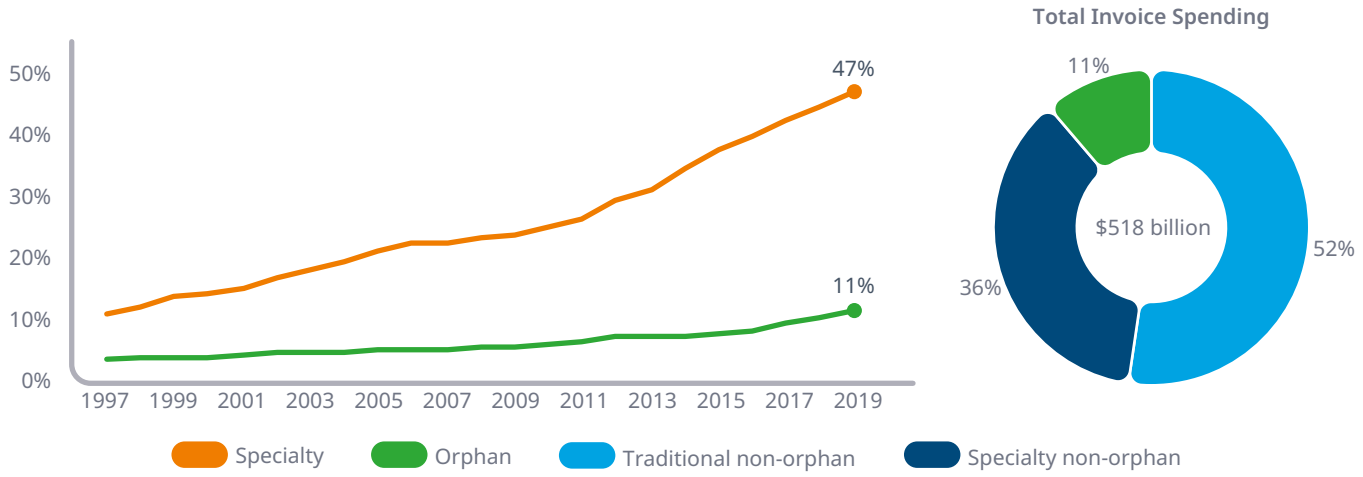
Source: IQVIA Institute, Aug 2020; FDA Orphan Drug Designations and Approvals[8]; IQVIA National Sales Perspective, Jan 2020

- Rare disease drug costs are varied, with treatments ranging from less than $6,000 per year to those over $500,0000 per year per patient. In 2019, the average annual cost of an orphan treatment per treated patient was $32,000.
- Currently, 61% of orphan drugs cost less than $100,000 annually, with the largest proportion of drugs costing between $6,000 and $50,000 per year.
- The second largest cost bracket is for orphan drugs that cost between $100,000 and $200,000 per year, with 81 drugs in this group.
- However, high cost therapies are generally prescribed for a small portion of patients. Of the rare disease patients treated in 2019, 52% were treated with drugs costing less than $50,000 per year, and 77% were treated with a drug costing up to $100,000 per year.
- Few patients receive medicines costing over $100,000 annually. Twenty-three percent of patients treated for a rare disease in 2019 received a medicine costing more than $100,000 annually. Less than 1% of rare disease patients received a drug with an annual cost over $500,000.

Exhibit Notes: Drugs with publicly stated or calculable annual costs were included. Audited data for 464, some of which may have ceased to be marketed, others may be outside scope of our data, leaving 389 drugs for this analysis (see Appendix, Methodology).

Since 2010, specialty medicine share of invoice spending increased from 25% to 47% as orphan spending share rose from 6% to 11%

Exhibit 11: Shares of Total Invoice Spending by Traditional, Specialty and Orphan Drugs in 2019, US$



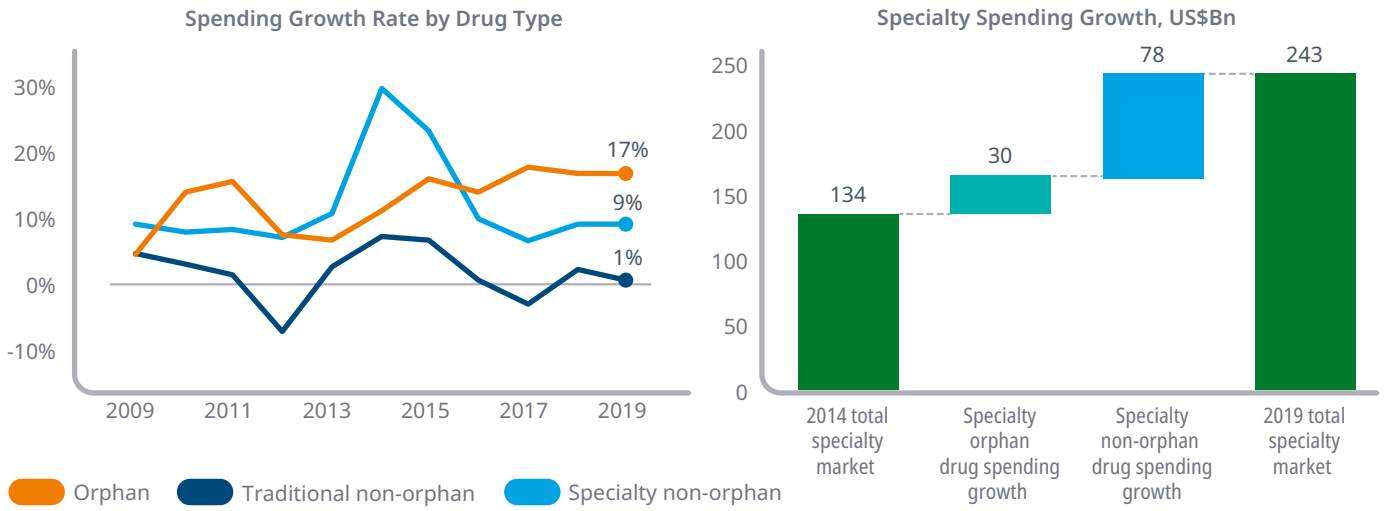
Source: IQVIA Institute, Aug 2020; FDA Orphan Drug Designations and Approvals[8]; IQVIA National Sales Perspective, Jan 2020

- Specialty medicines — those that treat chronic, complex or rare conditions, and require careful handling, complex patient management, or distribution (see Definitions for additional information) — now account for 47% of spending in the United States, an increase from 25% in 2010.
- Spending on orphan indications accounted for 11% of invoice spending in 2019. This is an increase from 6% in 2010. Invoice spending on orphan drugs includes all spending on orphan-only therapies as well as a proportion of sales from those drugs with both orphan and non-orphan indications.
- While there is a significant overlap between specialty and orphan drugs, 36 percentage points of the 47% specialty share, or $187 billion, are related to specialty non-orphan drugs in 2019.
- The traditional drug market has experienced price deflation due to the launch and uptake of a significant number of small molecule generics first launched in the 1990s. This price deflation in part drives the invoice spending share increase of specialty and orphan drugs over time.
- Of the specialty and orphan drugs available in 2019, many have launched within the past five years, and so still have market protections. Associated savings from small-molecule generics or biosimilars will not be realized in the immediate future.

Exhibit Notes: Specialty and Orphan shares are based on total market spending. Specialty and Orphan segments overlap, however some orphan drugs are considered traditional using IQVIA's specialty pharmaceutical definition. Orphan share includes factored orphan sales.

Orphan spending increased by over 14% per year since 2015, higher than the average annual growth rate for the rest of the market

Exhibit 12: Specialty, Orphan, and Traditional Invoice Spending Growth



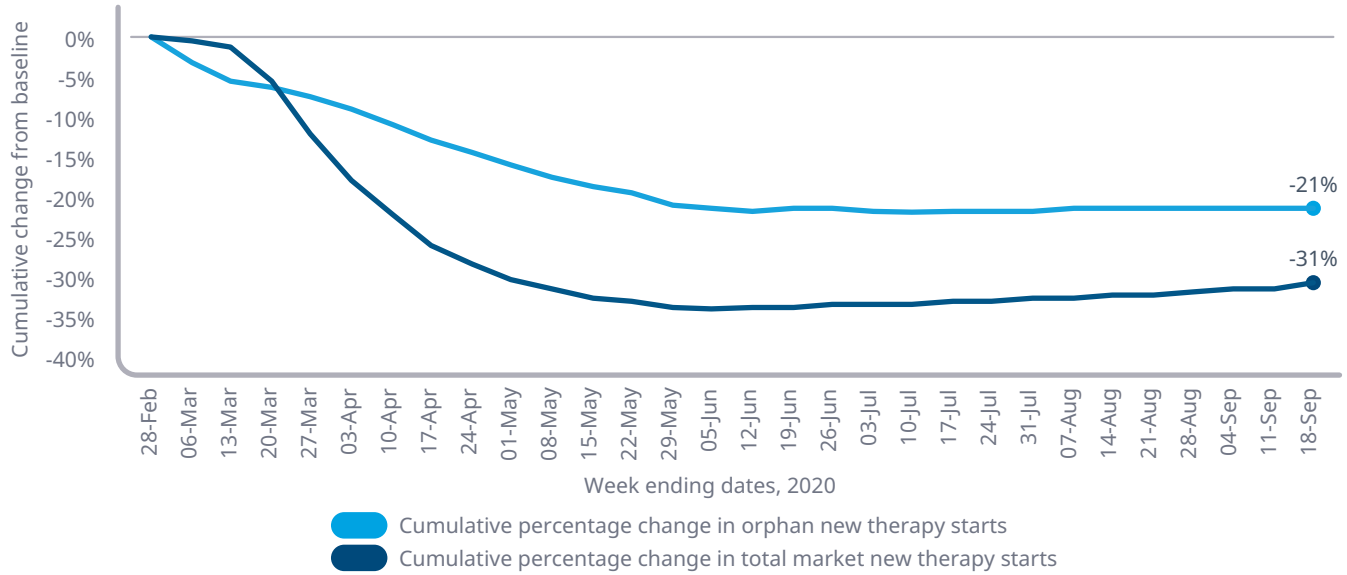
Source: IQVIA Institute, Aug 2020; FDA Orphan Drug Designations and Approvals[8]; IQVIA National Sales Perspective, Jan 2020

- The growth in invoice spending seen by orphan drugs has exceeded the total market significantly, with orphan drugs growing above 14% per year for the last five years, while the average annual growth rate for the rest of the market has been substantially lower.
- The specialty non-orphan market saw peak growth in 2014, reaching 30% growth on a year-over-year basis, but has declined since, with 9% growth in 2019.
- Similarly, the traditional non-orphan market saw a peak growth rate in 2014 of 7% year-over-year, with a declining trend in growth, reaching 1% year-over-year in 2019.
- Over the past five years, specialty medicines have grown from $134 billion in 2014 to $243 billion at invoice prices, with $30 billion of growth from orphan drugs.
- Non-orphan specialty drugs grew at a slower rate but added $78 billion in absolute growth over the same five years.
- Most of the growth in the overall pharmaceutical market has been associated with specialty and orphan drugs, with a greater amount of spending from non-orphan specialty drugs.

Exhibit Notes: Specialty and Orphan shares are based on total market spending. Specialty and Orphan segments overlap, however some orphan drugs are considered traditional using IQVIA's specialty pharmaceutical definition. Orphan share includes factored orphan sales. Totals may not sum due to rounding.

While new patients initiating orphan drug therapy are down 21% due to COVID-19, this segment is less affected than others

Exhibit 13: Cumulative Change from Baseline in Total Market and Orphan Drug New Therapy Starts During COVID-19



Source: IQVIA New to Brand Weekly, Sep 2020

- During the ongoing COVID-19 pandemic, new therapy starts (where a patient has not been on a treatment in the same therapy class in the last year) have been significantly affected, suggesting new orphan disease diagnoses are not occurring.
- Across the total market, new therapy start prescriptions are cumulatively down 31% from baseline, the eight-week period immediately preceding the COVID-19 pandemic in the United States.
- Orphan drug new start prescriptions have been more insulated from health system disruptions than other segments, with a cumulative decrease of 21% in new start prescriptions from baseline.
- As rare diseases typically go undiagnosed longer than more common diseases and require many physician visits to receive a confirmed diagnosis, COVID-19 could be delaying initial diagnosis for many patients with rare diseases.
- To date, almost 48,000 new therapy starts have not taken place, averaging 1,700 new orphan drug therapy starts per week.
- Notably, continuing orphan therapy appears more stable and can be attributed to the adherence of patients to treatment, provider and patient group outreach, and financial or logistical support from manufacturers and the government.
- In families with a member with a rare disease, financial burdens can be exacerbated, putting greater pressure and focus on financial support from stimulus payments, patient assistance or charities.

Exhibit Notes: Baseline number of new therapy start prescriptions was calculated as an average of the weekly new start prescriptions over an eight week period from week ending January 3, 2020 to week ending February 28, 2020.

Appendix

METHODOLOGY

Orphan spending was determined by identifying the amount of sales attributable to orphan and non-orphan indications of the same drug. A disease-specific factor was calculated by determining the size of the disease population based on 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). The factor was then applied to total sales in each year the drug was marketed, adjusting the factor as additional orphan indications were marketed.

Treated patient estimates are based on standardized dosing applied to audited sales. Audited sales are factored based on epidemiology of all approved indications to reflect the orphan uses of drugs with orphan and non-orphan approvals. Factoring includes real world data for the use of differing indications where possible, and published incidence or prevalence in the remaining instances.

Annual costs are researched using a combination of the most reliable sources available. Company statements about the annual cost are most commonly at list prices and reflect standard dosing from the medicine's approved label. If statements are not available, similar methods are used to derive an annual cost at standard dosing. Acute and episodic treatments are estimated based on a single cycle unless multiple cycles are noted as common.

Notes on sources

THIS REPORT IS BASED ON THE IQVIA SERVICES DETAILED BELOW

NATIONAL SALES PERSPECTIVES (NSP)™ measures revenue 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.

NATIONAL PRESCRIPTION AUDIT (NPA)™ is a suite of services that provides the industry standard source of national prescription activity for all products and markets across the retail, mail, and long term care channels.

IQVIA's NATIONAL PRESCRIPTION AUDIT: NEW TO BRAND (NPA NTB)
NPA New to Brand provides enhanced visibility into the volume of a patient's true, first-time use of a brand versus continued therapies. IQVIA's longitudinal data allows users to analyze new therapy starts, switched to/add-on products, as well as continued therapies. In addition to reporting the new or refill information from a prescription, the therapy history for the patient is taken into account in order to categorize that prescription. New to Brand RX (NBR) = New Therapy Start Rx + Switch/ Add-On Rx

IQVIA's MEDICAL CLAIMS DATA: Dx data are pre-adjudicated claims collected from office-based physicians and specialists. These data are sourced from CMS-1500 form-based claim transactions, the standard reimbursement form for all non-cash claims. Medical claims data includes patient-level diagnosis and procedures for visits to U.S. office-based individual professionals, ambulatory and general healthcare sites. The medical claims data includes more than 205 million patients, over 1.7 billion claims and 3 billion service records obtained annually.

MIDAS™ is a unique platform for assessing worldwide healthcare markets. It integrates IQVIA's national audits into a globally consistent view of the pharmaceutical market, tracking virtually every product in hundreds of therapeutic classes and provides 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™ PIPELINE INTELLIGENCE is a drug pipeline database containing up-to-date R&D information on over 40,000 drugs, and over 9,000 in active development worldwide. The database captures the full process of R&D, covering activity from discovery stage through preclinical and clinical development, to approval and launch.

ARK PATENT INTELLIGENCE is a database of biopharmaceutical patents or equivalents worldwide and including over 3,000 molecules. Research covers approved patent extensions in 52 countries, and covers all types of patents including product, process, method of use and others.

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Murray Aitken is Executive Director, IQVIA Institute for Human Data Science, which provides policy setters and decisionmakers in the global health sector with objective insights into healthcare dynamics. He led the IMS Institute for Healthcare Informatics, now the IQVIA Institute, 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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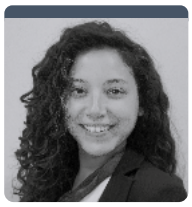

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Elyse Muñoz is a Thought Leadership Manager for the IQVIA Institute, managing aspects of IQVIA Institute research projects and conducting research and analysis within global healthcare. Elyse joined IQVIA in 2017 as an associate consultant in the Competitive Intelligence consulting group, where she developed rich clinical and commercial insights to serve million-dollar clients. She worked in major therapy areas including diabetes, cardiovascular disease and kidney dysfunction, as well as rare diseases such as hemophilia. Elyse holds a Bachelor of Science from Arizona State University in genetics, as well as a Ph.D. in genetics from Pennsylvania State University. Her research focused on understanding the genetic makeup of the parasite which causes malaria to aid in targeted drug development to help eradicate the disease.

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About the 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 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.

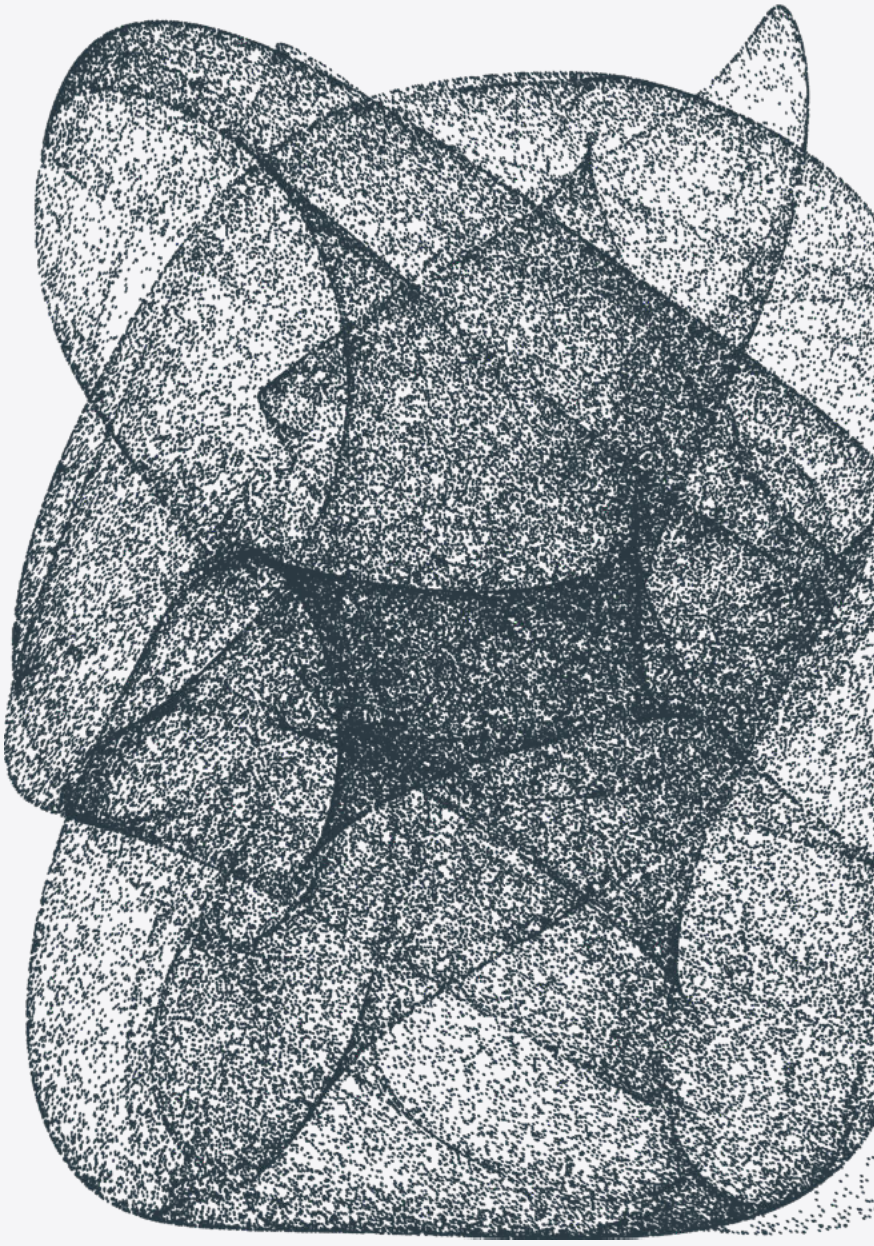
Guiding Principles

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 IQVIA Institute for Human Data Science is committed to using human data science to provide timely, fact-based perspectives on the dynamics of health systems and human health around the world. The cover artwork is a visual representation of this mission. Using algorithms and data from the report itself, the final image presents a new perspective on the complexity, beauty and mathematics of human data science and the insights within the pages.

The Algorithmic Art featured on this report cover is based on a time series of IQVIA data on orphan drug sales, volume, treated patients, and average annual cost of therapy from 1982–2019.



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