THE PRISM DOCTRINE

Disruption and Opportunity – The Abrupt Transition Toward Targeted Medicine

CROSSTREE

Table of Contents

Introduction

Built during the last century, the pharma services industry was primarily designed to develop, manufacture, distribute, and market conventional drugs. Such drugs have largely homogeneous logistical and economic characteristics, resulting in the industry developing mass-production efficiencies through economies of scale.

However, tomorrow's ecosystem must allow for more specialized, complex treatments and patient journeys, which will be tailored to each therapy in the case of stratified medicine, and to each patient with personalized medicine. Demands of specialty and targeted medicines are likely to be disruptive to established incumbents as they will require specialization, expertise, technologies, and agility that may not currently exist within such large, monolithic organizations. Furthermore, the economic model of specialty and targeted drugs may cause profound cultural disruption in the ecosystem of collaborators, competitors, and go-to-market playbooks.

This series of industry briefs takes an in-depth look at the transition of medicines from conventional, one-size-fits-all to targeted medicines, and how this transition is affecting the pharma services and diagnostics industry segments. We begin by quantitatively establishing the rapid transition of medicines from conventional to targeted medicines. To do this, we must first examine how we categorize drugs.

Historically, the drug research industry has classified drugs by therapeutic category. However, such classification obfuscates the significant and fundamental transitional trends taking place. Oncology, immunology, and CNS drugs, among others, are not monolithic treatments across the therapeutic area. For instance, classification of a drug as oncology does not distinguish between conventional (e.g., Axumin®), rare/orphan (e.g., Rituxan®), or precision (e.g., Tecentriq®).

Although data is available for examining specialty and precision medicines, this information is typically isolated from other segments or uses different datasets, which also confuses transition trends. Even so, instead of viewing data through the lens of therapeutic areas, we will establish a new viewpoint by observing data related to how and to whom the drugs are delivered. We call this the "Prism."

Categorizing medicines into conventional, specialty, or precision is the basis of the Prism. This foundational report defines these categories and quantifies the market. In the series of reports to follow, we will examine regulatory and market payer trends, as well as patient journeys, through the lens of the Prism in order to better understand the impact on pharmaceutical services companies, technologies, and diagnostic companies. In this way, we will illuminate the opportunities, advantages, and challenges likely to affect both incumbent and emerging providers.

Part I: Definitions and Medicine Characteristics

In our Prism, we have changed the lens we use to define medicine. We must also have a set of common definitions to fully understand the role that various medicines play in the U.S. and global health systems, both from a volume and a cost perspective. For the purposes of this report, the terms and medicine characteristics are outlined below.

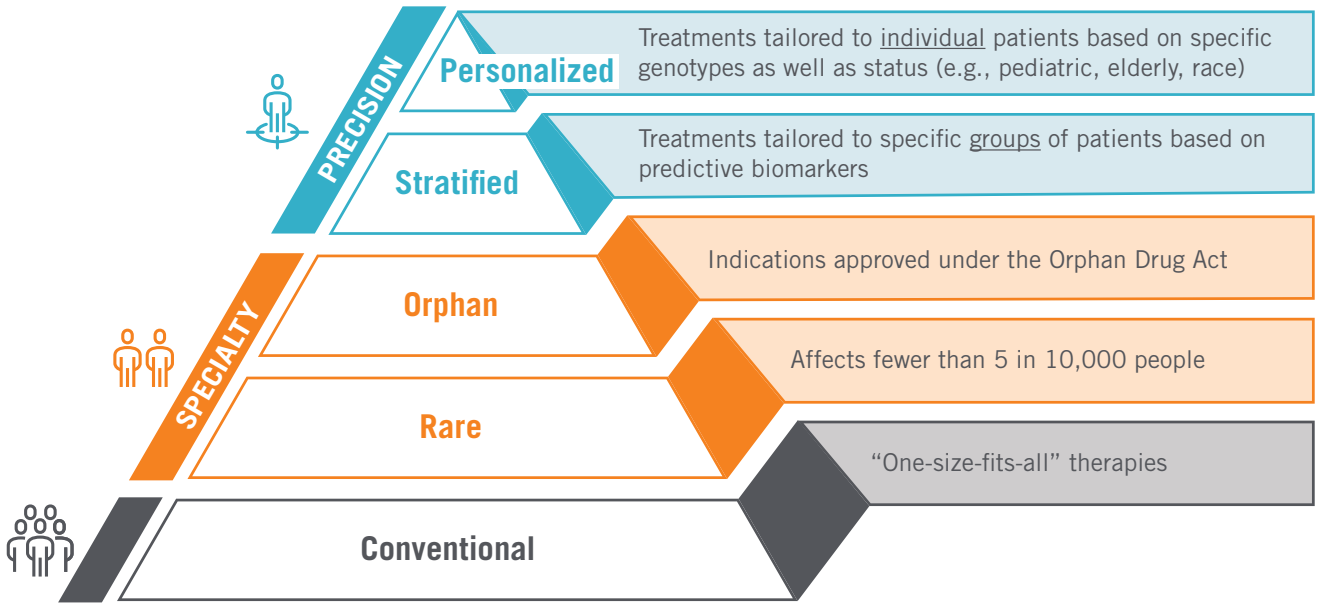


Figure 1: Prism segments

PRECISION MEDICINE

A quickly growing segment, precision medicine helps in the prevention as well as early diagnosis of patients, looking at the expression of genes or proteins and thus predicting response to specific medicines.[1] Twenty-five out of 59 new molecular entities (NMEs) approved by the FDA in 2018 were precision medicines.[2]

For our purposes here, we have adopted the definitions for precision medicine as stratified medicine, or personalized medicine as defined by the IQVIA Institute for Human Data Science.[3]

Stratified medicines require the use of predictive biomarkers to identify patient response or suitability to therapies. Individual patients in the patient group receive identical treatments. The bulk of precision medicines are stratified medicines.[4] An example is Depakote®, used to treat epilepsy and bipolar disorder, which has the largest volume among the stratified CNS therapies.

Along with stratified medicines, personalized medicines also fall under the precision umbrella. As defined by Crosstree, these medicines are tailored to individual patients based on specific genotypes as well as status (e.g., pediatric, elderly, race). Personalized medicines include gene therapies and many (but not all) immunotherapies.

Precision medicine improves the performance of health systems by aiming to improve patient centricity, and developing a better understanding of disease causes and treatment consequences, thereby providing measures to improve the quality and cost of health care being provided to patients.[5]

Specifically, precision medicine helps reduce costs associated with trial-and-error dosing, hospitalizations due to adverse drug reactions, late-stage health condition diagnoses, and reactive treatments. It can also play a crucial role in the implementation of value-based payment and delivery models, thus helping in the better coordination of patient care and cost reduction initiatives.[6]

While it is often thought that precision medicines are so specialized as to prohibit significant sales, that isn't always the case. Analysts expect a Novartis gene-therapy treatment for spinal muscular atrophy, which hasn't yet reached the market, to generate $1.7 billion in sales by 2023 and to become one of the first precision medicine blockbuster drugs.[7]

SPECIALTY MEDICINE

Specialty medicines, as defined by Crosstree, are those medicines that (i) treat rare diseases, (ii) are classified as orphan drugs by the Food and Drug Administration (FDA), (iii) require special handling due to low volume, cold-chain, or other storage requirements, or are managed through separate organizational or delivery channels, including specialty pharmacies, (iv) are difficult or complex to manufacture on a consistent basis, or (v) require additional monitoring by a physician or are required to be initiated by a specialist.

Comprising both injectable and non-injectable drugs, specialty medicines are used to treat chronic, complex conditions.[8] These medicines have characteristics that can include: limited distribution network(s), close patient monitoring, requirements for special handling, complex formulations and/or manufacturing techniques, high costs per unit, and use in small or unique patient populations.[9]

Most often, specialty medicines are used to treat rare diseases. Crosstree has adopted the National Institutes of Health (NIH) definition of rare disease as one that affects fewer than 200,000 people in the United States, and further expands the definition to include diseases that affect fewer than 5 in 10,000 of the general population globally. There are nearly 7,000 rare diseases, and more than 25 million Americans have one.[10] Roughly 3.5-5.9% of the global population is affected by a rare disease, which equates to 263-446 million persons affected at any point in time.[11]

Rare diseases are acute or chronic in nature and may be considered life-threatening. They include cancers such as childhood cancers and some other well-known conditions, such as cystic fibrosis and Huntington's disease. Significant research is still required to learn more about the pathophysiology and natural course of these diseases, and epidemiological data remain limited or not available in many cases. Drug recovery costs are less in the case of rare disease for pharmaceutical companies, so, clinical trial funding programs continue to be an essential component motivating orphan drug development.[12]

The distinction between rare disease medicines and orphan drugs is a small one, and the terms are often used interchangeably. Crosstree defines orphan drugs as those medicines with one or more indications approved under the 1983 Orphan Drug Act (ODA) — which includes drugs for rare diseases and also for other indications, essentially drugs that cannot be manufactured and marketed profitably. Crosstree further expands this category to include those drugs associated with a patient pool of less than 0.1% (for the U.S.); this may include drugs approved for non-orphan indications.

In 2018, around 34 novel new drugs for rare disease were approved by the FDA's Center for Drug Evaluation and Research (CDER) — a number driven by the incentives provided by the ODA. These incentives include an R&D tax credit for 25% of clinical trial costs, seven years of market exclusivity, and federal funding through a variety of grants to perform the required clinical trials.[13] The success of that legislation led to similar incentives being adopted in other key markets, most notably in Japan in 1993 and in the European Union in 2000.

While these changes have successfully encouraged companies to invest in these treatments, patients with rare diseases continue to bear a large portion of the health care burden from the effects of their disease as well as direct and indirect budgetary issues. For example, they may require more expensive medical tests and more frequent visits to multiple specialists, impacting the cost of overall treatment and increasing their financial burden and that of the overall health care system. Diagnosis, too, is often delayed largely due to a lack of awareness and knowledge by the various health care stakeholders.

Furthermore, there is an inverse relationship between the price of these therapies and their volume of use: Orphan drugs are developed for small patient populations, making them expensive for both patients and payers. For example, the median annual cost for an orphan drug in 2017 was over $46,800, while the median annual cost for the top 10 disease therapies used by the greatest number of patients was $1,216.

Thus, drug spending in the U.S. is progressing from a prominence on high-volume, low-cost drugs for chronic diseases to low-volume, high-cost drugs with higher value in terms of patient outcomes.[14]

CONVENTIONAL MEDICINE

Crosstree defines conventional medicines as all drugs that do not meet the criteria to be exclusively classified as specialty or precision medicines. Such medicines are pharmacologic therapies that have a one-size-fits-all, bell-curve approach to targeting large patient populations. The health care delivery model followed by conventional medicine can be primary, secondary, or tertiary care. Health care stakeholders use the traditional physical examination for the diagnosis of disease or medical signs of disease, using methods like inspection, palpation, percussion, and auscultation.

Conventional medicine focuses on vast varieties of disease areas and has a huge patient pool, unlike specialty or precision medicine. Conventional medicine will usually fall under the normal reimbursement process and has minimal or no out-of-pocket costs for patients. This includes treatment of acute and chronic illnesses, preventive care, and health education irrespective of the patient group, age, therapy area, or even more specific factors like genetics.

While gene therapies and certain immunotherapies are excluded from conventional medicines, conventional medicines can include both large and small molecules drugs.

Examples of conventional medicines include nearly all blockbuster drugs that generate or generated sales of at least $1 billion (all dollar values in USD), such as Lipitor® (for high cholesterol), Humira® (a multi-label immunosuppressive), Advair® (for chronic obstructive pulmonary disease (COPD)), and Zoloft® (for depression).

Immunotherapy Prism Classification

Immunotherapy refers to a therapy that stimulates or suppresses the immune system to help the body fight cancer, infections, or any other disease. Immunotherapy can be classified as either conventional or precision medicine using the Prism classification.

CONVENTIONAL MEDICINE

If the therapy targets certain cells in the immune system or is a general target for the general population, the immunotherapy is classified as conventional medicine. Examples include cytokines, vaccines, bacillus Calmette-Guerin (BCG), and some monoclonal antibodies.[15] Other common examples of immunotherapy used in conventional medicine include the chickenpox vaccine and seasonal flu shots.

PRECISION MEDICINE

In precision medicine, the immunotherapy drug uses specific target pathways to modify the course of disease in specific patient populations. Precision drugs can be stratified or personalized.[16]

An example of immunotherapy working as a stratified medicine (in a specific group of people) is Ninlaro®. Approved for multiple myeloma, Ninlaro® is more effective for white Americans than African Americans.[17]

When immunotherapy, including cell-based or gene-based therapies, acts upon a specific genetic type, it is classified as personalized medicine. For example, Imlygic®, a genetically engineered viral therapy for the local treatment of recurrent melanoma, causes lysis of tumor cells followed by release of tumor-derived antigens, which together with virally derived GM-CSF may promote an antitumor immune response.[18]

Within personalized medicine, gene therapy treats the underlying cause of the disease in an individual patient by altering the genetic code. Gendicine®, for example, is a specialized gene therapy medicine to treat cancer by using a shuttling system based on adenovirus to carry a p53 gene to limit cancer growth. A diagnostic test is performed by PCR-based next generation sequencing of DNA to examine the mutation status of the entire coding region of the WTP53 gene.[17]

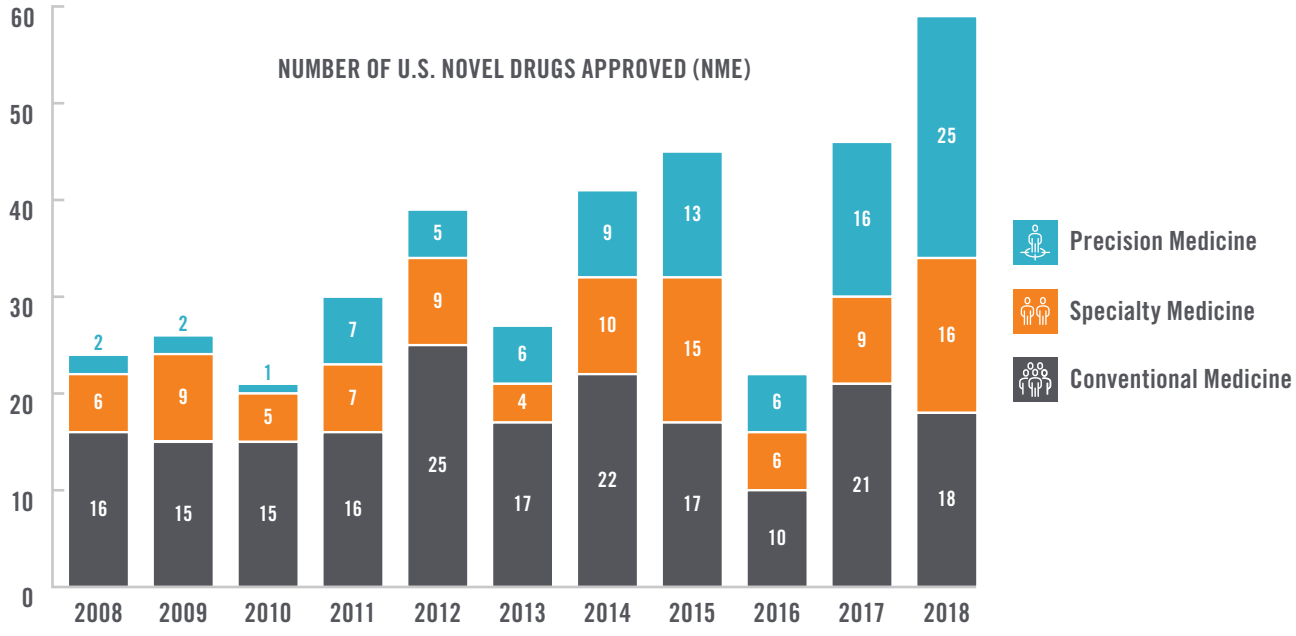
Part II: The Transition

MEDICINE APPROVALS BY CATEGORY

With the terms and characteristics defined, we turn our attention to the approval rates to demonstrate the industry's rather abrupt transition away from conventional medicine.

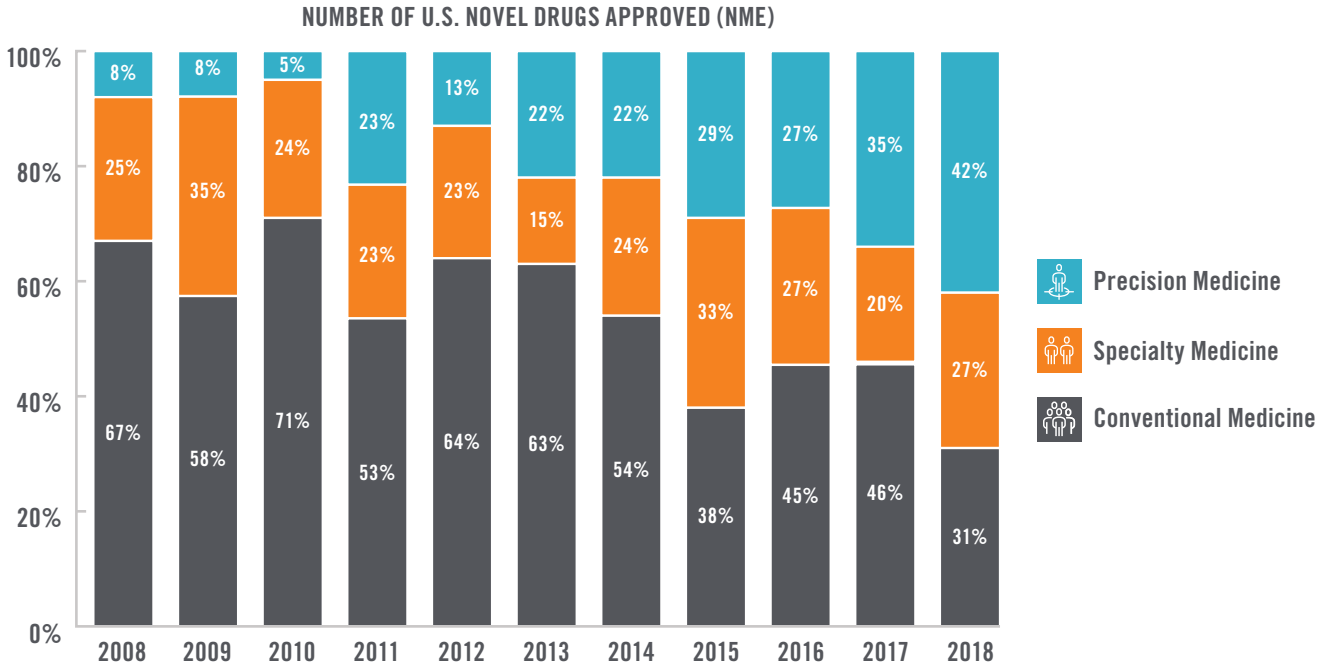
Crosstree's initial efforts to classify medicines by Prism category were met with significant challenges. First, drugs can be labeled for multiple indications, some of which may be classified as conventional and others as specialty or precision. Furthermore, the quality of data available to classify medicines by Prism category varies by country. Ultimately, we determined that the U.S. FDA has the most consistent and reliable data in order to best segment drug approval by Prism category.

In 2008, 8% of the new molecular entities approved by FDA were precision medicine, whereas in 2018, 42% of the new molecular entities approved by FDA were precision.[19] From 2013 to 2018, 69 precision medicines were approved by the FDA, which constitutes 75% of the total precision medicines approved through the end of 2018 — a significantly higher number of approvals than the 2008 to 2013 time frame when 42 novel precision medicines were approved, constituting 25% of the total approval of precision medicine through the end of 2018.[20]



Source: Crosstree

Biopharmaceutical companies nearly doubled their R&D investment in precision medicines over the past five years and expect to increase their investment by an additional 33% in the next five years. Furthermore, 42% of all compounds and 73% of oncology compounds in the pharmaceutical pipeline have the potential to be precision medicines.

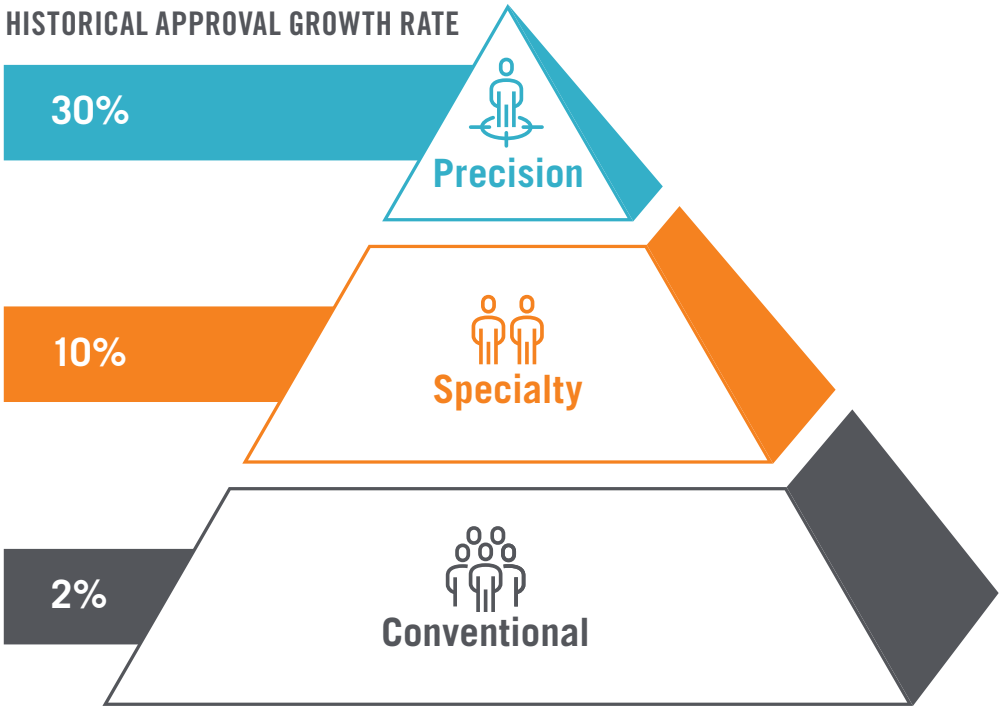


Source: Crosstree

While the growth rate in approved medicines is strong in specialty, it is exceptionally so in precision. At the same time, conventional medicine approval growth has slowed to a near-standstill. From 2008 to 2013, conventional medicine averaged 17 approvals per year. From 2014 to 2018, average approvals were 18, an increase of 6%.

While conventional medicine growth has been relatively stagnant, growth in approved medicines has been exceptionally concentrated in targeted medicine. From 2008 to 2013, specialty medicine had an average of seven approvals per year. From 2014 to 2018, average approvals jumped to 11 — an increase of 60%. Similarly, from 2008 to 2013, precision medicine averaged four approvals per year. From 2014 to 2018, precision medicine averaged 14 approvals per year — an increase of 250%.

Using the historical approval growth rate from 2009 to 2018, the Prism is further refined below:



Source: Crosstree

Part III: Market Size and Growth

PRECISION MEDICINE

The precision medicine market is a multibillion-dollar market consisting of many companies involved in the research and development, manufacturing, and commercialization of novel drugs and diagnostic tests. The global precision medicine market was valued at $52.6 billion in 2018 according to Global Market Insights.[21] The same report estimates that the market for precision medicines will grow at a compound annual growth rate (CAGR) of approximately 11% from 2019 to 2025.

Market growth is being propelled by an increasing demand for personalized treatments, technological innovations, and advancements including biomarker-based tests/kits, next gene sequencing, and AI-enabled imaging, as well as increased/favorable government support and regulations — all of which have significantly helped in creating increased demand for precision medicine solutions. According to Global Market Insights, the United States and certain European countries are currently the major hubs for conducting and recruiting patient pools used in precision medicine trial applications in oncology, globally.[22]

SPECIALTY MEDICINE

According to EvaluatePharma's Orphan Drug Report 2019, the worldwide market for orphan drug sales was approximately $131 billion in 2018,[23] and is expected to grow at a CAGR of 12.3% from 2019 to 2024. Persistence Market Research estimates the global market for rare diseases was approximately $102 billion in 2017,[24] suggesting a global specialty market of approximately $233 billion. Persistence Market Research predicts the global populations for rare diseases will grow at a CAGR of 8.6% from 2017 to 2025, suggesting a weighted-average growth rate of approximately 10.7%.

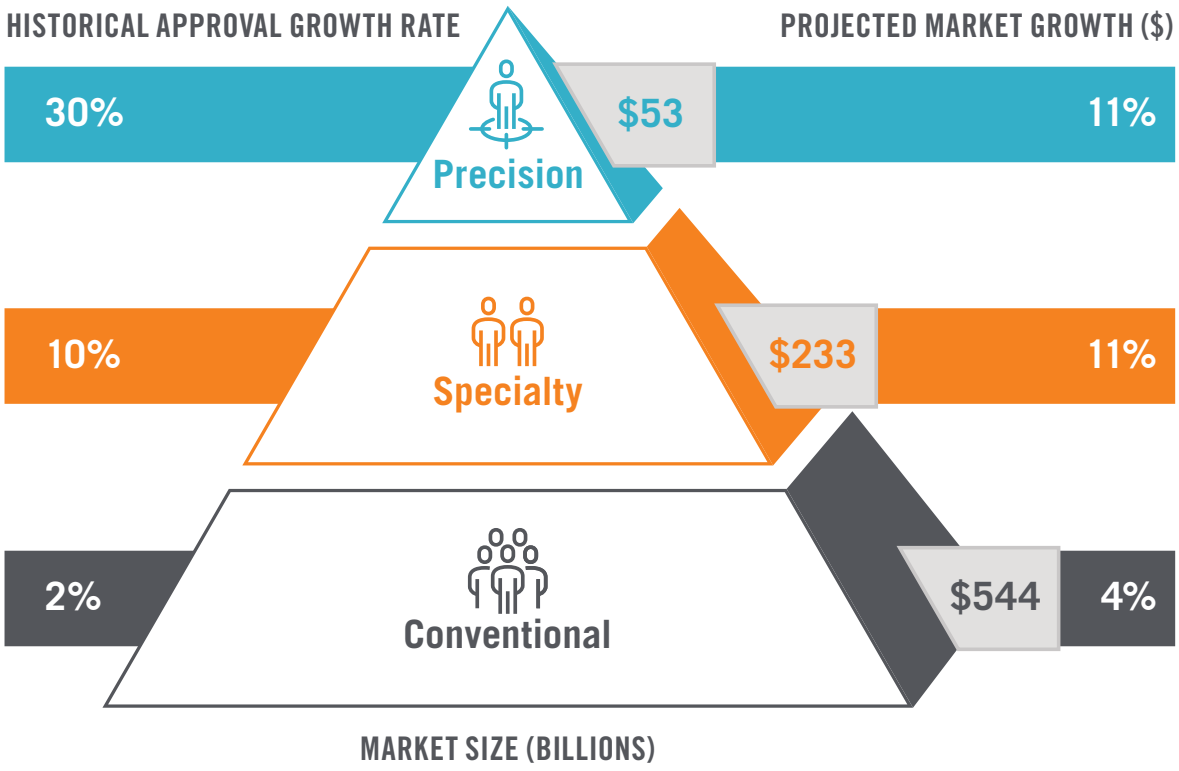
IQVIA estimates the U.S. orphan drug spending market in 2017 was approximately $43.1 billion,[25] and the total specialty market in the U.S. was approximately $194.4 billion.

CONVENTIONAL MEDICINE

EvaluatePharma gauges total worldwide prescription drug sales — including conventional, specialty, and precision — were approximately $830 billion in 2018, with a consensus forecast to grow at a CAGR of 6.5% through 2022.[26] Therefore, Crosstree estimates the global market for conventional medicine to be approximately $544 billion, after removing the estimated market sizes for specialty ($233 billion) and precision ($53 billion), with an expected CAGR of approximately 4% through 2022.

Part IV: Conclusion

Over the last decade, the pharmaceutical industry has rapidly evolved from a model of developing blockbuster drugs for large patient populations into a market delivering targeted medicines to narrow population segments. The anticipated growth rate in these targeted medicines is expected to increase almost three times faster than for conventional medicines.



Source: EvaluatePharma, IQVIA, Crosstree

The transition to targeted medicine will result in a renaissance for the pharma services industry. Patient centricity may (at last) become reality as specialty and boutique providers compete with incumbents by offering innovative solutions to personalized patient journeys. Incumbents will no longer be able to rely upon global scale and critical mass to maintain market share. And legacy providers that fail to adapt and innovate will be rapidly eclipsed by competitors.

For a highly regulated and notoriously conservative industry, these circumstances represent a profound and abrupt shift. By examining these changes through our Prism, our continuing white paper series will provide incumbents and emerging providers insights to allow them to evaluate for themselves not just how to respond to, but also how to proactively meet, the challenges of this rapidly changing market.

Endnotes

1 Aitken, Murray, and Michael Kleinrock. "Medicine Use and Spending in the U.S.: A Review of 2018 and Outlook to 2023" *IQVIA Institute for Human Data Science,* May 2019. www.iqvia.com/insights/the-iqvia-institute/reports/medicine-use-and-spending-in-the-us-a-review-of-2018-and-outlook-to-2023. Accessed 3 Dec. 2019.

2 "Personalized Medicine at FDA: A Progress & Outlook Report." *Personalized Medicine Coalition,* Jan. 2019. www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/PM_at_FDA_A_Progress_and_Outlook_Report.pdf. Accessed 3 Dec. 2019.

3 Aitken, Murray, and Alana Simorellis. "Upholding the Clinical Promise of Precision Medicine." *IQVIA Institute for Human Data Science,* May 2017. www.iqvia.com/insights/the-iqvia-institute/reports/upholding-the-clinical-promise-of-precision-medicine-current-position-and-outlook. Accessed 3 Dec. 2019.

4 Ibid.

5 Aitken, Murray. "The Global Use of Medicine in 2019 and Outlook to 2023." *IQVIA Institute for Human Data Science,* 29 Jan. 2019. www.iqvia.com/insights/the-iqvia-institute/reports/the-global-use-of-medicine-in-2019-and-outlook-to-2023. Accessed 3 Dec. 2019.

6 "The Personalized Medicine Report." *Personalized Medicine Coalition*, 2017. www.personalizedmedicinecoalition.org/Userfiles/PMC-Corporate/file/The-Personalized-Medicine-Report1.pdf. Accessed 3 Dec. 2019.

7 Grant, Charley. "The Side Effects of Million-Dollar Drugs." *The Wall Street Journal*, 1 Mar. 2019. www.wsj.com/articles/the-side-effects-of-million-dollar-drugs-11551447001. Accessed 3 Dec. 2019.

8 Drug Trend Report. Express Scripts, 2017.

9 "Specialty Medications." *National Pharmaceutical Services*, legacy.pti-nps.com/nps/index.php/specialty-medications/. Accessed 3 Dec. 2019.

10 "Rare Diseases." *MedlinePlus, U.S. National Library of Medicine,* 22 May 2019. medlineplus.gov/rarediseases.html. Accessed 3 Dec. 2019.

11 Wakap, Stéphanie Nguengang, et al. "Estimating Cumulative Point Prevalence of Rare Diseases: Analysis of the Orphanet Database." *European Journal of Human Genetics,* 16 Sept. 2019. doi:10.1038/s41431-019-0508-0.

12 "Priority Medicines for Europe and the World Update Report." *World Health Organization,* World Health Organization, 20 Nov. 2015. www.who.int/medicines/areas/priority_medicines/en/. Accessed 3 Dec. 2019.

13 "Spurring Innovation in Rare Diseases." *Pharmaceutical Research and Manufacturers of America,* 28 Feb. 2019. www.phrma.org/Fact-Sheet/Spurring-Innovation-in-Rare-Diseases. Accessed 3 Dec. 2019.

14 Aitken, Murray, and Michael Kleinrock. "Orphan Drugs in the United States (Part One)." *IQVIA Institute for Human Data Science,* Dec. 2018. www.iqvia.com/insights/the-iqvia-institute/reports/orphan-drugs-in-the-united-states-growth-trends-in-rare-disease-treatments. Accessed 3 Dec. 2019.

15 US National Library of Medicine, National Institutes of Health website. www.cancer.gov/publications/dictionaries/cancer-terms/def/immunotherapy. Accessed 11 March 2019.

16 IQVIA Institute for Human Data Sciences, Upholding the Clinical Promise of Precision Medicine. May 2017.

17 Chen, Caroline, and Riley Wong. "Black Patients Miss Out On Promising Cancer Drugs." www.propublica.org/article/black-patients-miss-out-on-promising-cancer-drugs. Accessed 11 March 2019.

18 Imlygic®, prescribing information, Amgen website. www.imlygichcp.com/mechanism-of-action/. Accessed 11 March 2019.

19 *The Personalized Medicine Report.* Personalized Medicine Coalition, 2017.

20 *The Personalized Medicine Report.* Personalized Medicine Coalition, 2017.

21 Ugalmugale, Sumant. *Precision Medicine Market Share Forecasts.* Global Market Insights, 2019.

22 Ibid.

23 *Orphan Drug Report 2019.* 6th ed., EvaluatePharma, 2019.

24 *Global Market Study on Rare Disease Treatment.* Persistence Market Research, 2017.

25 "Orphan Drugs in the United States (Part 1), *IQVIA Institute for Human Data Sciences,* October 2018.

26 *World Preview 2018, Outlook to 2024.* 11th ed., EvaluatePharma, June 2018.