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Outlook for Global Medicines through 2021

Balancing Cost and Value

Introduction

Medicines are advancing at an astonishing rate, as are the challenges in funding access to them for countries around the world faced with slowing economic growth and limited resources. Each part of the world is facing these challenges and addressing them differently.

In this report, we provide an outlook on the use of medicines and spending levels through 2021. Over the next five years, we expect to see a historically large number and quality of new medicines emerge from the research and development pipeline. In addition, we expect that issues of pricing, access and priorities will come to the forefront like never before.

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Executive summary

The total volume of medicines consumed globally will increase by about 3% annually through 2021, only modestly faster than population and demographic shifts, but driven by very different factors around the world. Spending on medicines will grow by 4–7%, primarily driven by newer medicines in developed markets and increased volume in pharmerging markets. Developed markets will offset increased costs from new medicines with the use of generics, and a greater focus on pricing and access measures, while pharmerging markets will struggle to live up to promised access expansions made when their economic outlooks were stronger.

By the numbers

Global medicine spending will reach nearly $1.5 trillion by 2021 on an invoice price basis, up nearly $370 billion from the 2016 estimated spending level. Importantly for the outlook is that spending growth is slowing in 2016, declining from nearly 9% growth in 2014 and 2015 to just 4–7% CAGR over the next five years. The short-term rise in growth in 2014 and 2015 was driven by new medicines in hepatitis and cancer that contributed strongly to growth but will have a reduced impact through 2021. Most global spending growth, particularly in developed markets, will be driven by oncology, autoimmune and diabetes treatments where significant innovations are expected. The U.S. will continue as the world's largest pharmaceutical market and pharmerging markets will make up 9 of the top 20 markets. China will continue as the #2 market, a rank it has held since 2012. Developed market spending growth will be driven by original brands, while pharmerging markets will continue to be fueled by non-original products that make up an average 91% of pharmerging market volume and 78% of spending. New medicines increasingly are specialty in nature, and their share of global spending will continue to rise from less than 20% ten years ago to 30% in 2016 and to 35% by 2021, approaching half of total spending in U.S. and European markets. This rise primarily will be driven by the adoption of new breakthrough medicines, but also will be a key focus of payers and constrained by cost and access controls as well as a greater focus on assessments of value. Off-invoice discounts and rebates, particularly in the U.S. market, will reduce invoice-price growth by about 1%, resulting in a total global market of $1 trillion in 2021.

Transformations in disease treatment

The number of new medicines reaching patients will be historically large with 2,240 drugs in the late-stage pipeline and an expected 45 new active substances (NAS) forecast to be launched on average per year through 2021. The new medicines will address significant unmet needs in cancer, autoimmune diseases, diseases of the metabolism, nervous system and others. In addition to the continued research of mechanisms in use in existing drugs, there will be an ongoing flow of new mechanisms to target cell processes and diseases across the spectrum. Developments that go beyond specific "drugs" are emerging in research that will challenge traditional regulatory

approval and commercialization approaches. These include completely new platforms that will see their first human uses in areas such as gene-editing technology CRISPR, which could transform personalized cancer treatments while creating a plethora of ethical dilemmas. Advances are expected to treat a range of diseases by harnessing the microbiome (a person's own gut bacteria), as well as regenerative cell technologies that include stem cells harvested from one part of the body to use against a disease in another.

Cancer is by far the largest general category of research, including immunology, cell-therapy and dozens of molecularly targeted agents. Treatment choices will be made based on the tumor diagnosis as much as by a patient's family history, genetic marker or by biomarkers the tumor expresses. The sheer number of cancer treatments, their potential combinations in treatment regimens, and the variety of companies involved in development will bring significant change to the landscape of cancer treatment over the next five years. Dramatic improvements in survival and tolerability are expected and will be accompanied by substantially greater levels of clinical trial and real-world information to support treatment decisions. Payers and providers are developing tools to better assess value and will demand, or create on their own, the evidence to support spending, especially where new treatments would add to already expensive cancer treatment costs.

Trends in U.S. medicines

U.S. market growth will slow by half in 2016 to 6–7% from 12% in 2015, and is forecast to average 6–9% through 2021. This decline is a key driver of the overall global slowdown and has similar causes—the end of Hepatitis C-driven growth and the greater impact of patent expiries after a period with fewer brand losses of exclusivity. U.S. growth also was lifted in 2014 and 2015 by historically high price increases for both brands and generics on an invoice-price basis before the impact of off-invoice discounts and rebates. After adjusting for those price concessions by manufacturers, spending growth is estimated to be more than 4 percentage points lower in 2016 and 2 percentage points lower through 2021, growing at a 4–7% CAGR. Pricing, and particularly the difference between invoice and net prices, will be a key political issue for the incoming administration but is unlikely to affect the forecast net growth rates.

Medicine costs will be driven by the use of transformative specialty brands and invoice price increases, offset by rebates and the use of lower-cost generics. Brand prices will increase at 8–11%—more slowly than the 12–15% in the past 3 years, and with fewer outlier major price increases as these have become unsustainable in light of high-profile media and political attention. Net prices for protected brands are expected to increase, albeit at a slower 2–5% rate, and including some declines for products facing greater competition and price transparency.

Patient out-of-pocket costs are forecast to decline despite rising brand prescription costs as patients shift to newly available generics and receive copay assistance for brands. More than one-third of prescriptions will have no out-of-pocket costs. Free prescriptions are a growing trend as some patients receive preventive services under the Affordable Care Act, under expanded eligibility for Medicaid, and through some insurance plans.

The reduction in overall spending as branded medicines lose exclusivity is expected to total $143.5 billion in the next five years—more than 1.5 times the impact as in the past five years. This includes the estimated impact of biosimilars, which will contribute between $27–58 billion, uncertainty based on multiple issues in litigation with originators, as well as regulatory, pricing and competitive dynamics. Regardless of the uncertainty, biosimilars are expected to affect spending over the next five years, with 25–35 products in development across biologic molecules with the highest sales levels.

Pricing and growth in Europe

Low pre-rebate and discount growth of 1–4% in the EU5 countries through 2021 is partly driven by policymaker responses to unexpectedly high new drug spending growth in 2014 and 2015, and efforts to control future growth. The Hepatitis C drugs were surprising to stakeholders in their effectiveness, the extent to which patients and providers were willing to use them, and the budget impact that few were able to accurately predict. Looking forward, these budgeting weaknesses are prompting European payers to redouble their efforts to bring predictability to their budgeting processes for drugs—especially given the wave of promising agents to treat a variety of diseases. Mechanisms that control access based on clinical quality alone may not be sufficient in the face of the variety and number of breakthroughs expected.

Perhaps the most pressing question for European governments on issues outside pharma center around BREXIT. The more than half-century of progressively greater integration of Europe including medicines-related institutions and practices will make disentangling the U.K. from Europe extremely complicated, not least because the U.K. government has yet to officially trigger the process. While uncertainties remain, the impact on the U.K. pharmaceutical market is expected to be modest with a 1.5% slower growth rate in the downside scenario, than the basecase outlook for 4–7% growth to 2021, still the highest medicine spending growth in the EU5 in either case.

Relatively weak economic growth in the region, combined with budget concerns arising from adopting and paying for recent innovations, will encourage European payers to be more cautious in adopting newer medicines in the future. Mechanisms to control price and/or access to innovative drugs continue to be the main tools used by European governments to manage spending on medicines, and will limit spending growth through the forecast period. As a result, fewer new launches in Europe are achieving price premiums, as few medicines are considered breakthroughs while the remainder are subject to more stringent levels of price limitations at launch.

Medicine use in pharmerging markets

Since 2011, the global expansion in the volume of medicines used essentially has been driven by pharmerging markets, where volume grew 37.5% over five years, or 7% annually, compared with 2% in total over five years in all other markets.

In most developed markets, where access already was high and usage driven by demographic shifts to aging populations, volume grew an average of 0.4%—less than half the rate of population growth in most markets. In pharmerging markets a decade ago, many lacked basic healthcare infrastructure and patients often paid for medicines out-of-pocket without insurance coverage. As access expanded through government support of expanded infrastructure and either government or private insurance coverage, medicine usage expanded broadly. More recently, as economic growth has slowed, medicine volume growth also has slowed, showing a direct correlation between medicine usage and affordability.

Compared to ten years ago with the start of their growth boom, leading pharmerging markets have seen real GDP growth slow from 1 to 4 percentage points, and their currencies' value to the U.S. dollar weaken by 15–35%. Medicine spending growth has slowed from 2–10 percentage points over the past five years in major pharmerging markets and is expected to slow further. Volume growth averaged 7% for pharmerging markets over the past five years but is expected to slow to 4% through 2021, as China declines from 17% average annual volume growth in the past five years to 4% CAGR in the five years through 2021. Broad economic issues have led to a range of derailed commitments and delayed, revamped or cancelled expansion programs—initiatives that may be hard to restart even if economic conditions recover.

Overall, volume growth continues to be driven by non-original products that account for 91% of volume in pharmerging markets, and the outlook for spending growth across these markets is expected to be slower in the next five years and beyond.

By the numbers

- Global medicine spending will reach nearly $1.5 trillion by 2021
- Growth will slow from nearly 9% in 2014 and 2015 to 4–7% over the next five years
- Hepatitis C treatments which drove 2–3% points of growth in 2014 and 2015 will have a reduced impact to 2021
- Oncology, autoimmune and diabetes treatments will drive much of the growth
- The U.S. will continue as the world's largest pharmaceutical market and pharmerging markets will make up 9 of the top 20 markets with China as #2
- Developed market spending growth will be driven by original brands while pharmerging markets will continue to be driven by non-original products
- Innovation in specialty medicines will continue lifting the share of global spending from 30% in 2016 to 35% in 2021
- Specialty medicines will approach half of medicine spending in the U.S. and EU5, driven by the adoption of new breakthrough medicines and constrained by cost and access controls and a greater focus on assessments of value
- Global spending growth will be driven by branded products in developed markets, offset by the impact of patent expiries and off-invoice discounts and rebates, particularly in the U.S. market

Global medicine use and drivers of growth

Global spending on medicines will reach nearly $1.5 trillion in 2021 growing at 4–7 %—only slightly slower than the 5.9% growth over the past five years, but with growth expected to be more uniform and predictable in nature (see Exhibit 1). The last five years included two of the most unusual events in the history of the industry—the so-called "patent cliff" and the launch in quick succession of effective cures for Hepatitis C (Sovaldi and Harvoni), which became the two most successful new medicine launches of all time. The next five years will see the market growing at a more consistent rate but with much more attention focused on spending, growth and specifically pricing (see Exhibit 1).

Notable in 2014 and 2015 were not only the Hepatitis C launches, which captured global attention, but also the significant currency fluctuations for major global currencies against the U.S. dollar. Global pharmaceutical spending grew by 8.8% in 2015 on a constant U.S. dollar basis, which removes the impact of currency exchange rates, equivalent to $85.7 billion. Exchange rate effects reduced that growth to $7.4 billion (see Exhibit 1).

The continued growth of global medicine spending over the past decade and the next five years will more than double the amount spent on medicines over that fifteen year period. Over that timeframe the drivers of medicine spending and growth have shifted from the blockbuster drugs of the late 1990's, to the volume-driven growth in pharmerging markets and the developed markets patent cliff, and over the next five years to a continued boom in innovation-driven spending growth for breakthrough immunology treatments across a range of diseases.

Exhibit 1: Global Market Spending and Growth 2007–2021

Source: IMS Market Prognosis, Sep2016; QuintilesIMS Institute, Oct 2016

Key therapy areas driving spending and growth over the next five years will be led by oncology, reaching $120–135 billion in spending in major developed and pharmerging markets (see Exhibit 2). Oncology spending will grow at 9–12%, largely similar to the last five years, driven by continued wave of immune-oncology treatments with dramatically improved outcomes and tolerability for patients.

Diabetes treatments continue to evolve with new more convenient formulations, combinations and delivery systems expected in the next five years as well as the wider adoption of biosimilars in major developed markets. The combination of continued innovation, disease prevalence and biosimilars will see diabetes spending reach $95–110 billon by 2021, up an average 8–11% over the next five years.

Biologic treatments for autoimmune diseases, including treatments for rheumatoid arthritis, psoriasis, ulcerative colitis, Crohn's disease and a range of related disorders continue to see increasing usage across geographies and will reach $75–90 billion in spending by 2021, up 11–14%. There are a range of new treatments in development which will stretch the definition of autoimmune diseases to include additional dermatological, gastrointestinal and pain related conditions. In addition, biosimilar products—those approved as similar to an originator reference biologic product—will be available for several of the leading autoimmune products by 2021, potentially allowing wider use of these medicines with the same or lower overall spending.

Exhibit 2: Outlook of Leading Therapy Areas Spending and Growth, Constant US$Bn

Therapy Areas	Spending 2016	2011–16 CAGR	Spending 2021	2016–2021 CAGR
Oncology	75.3	10.9%	120–135	9–12%
Diabetes	66.2	16.4%	95–110	8–11%
AutoImmune	45.1	18.2%	75–90	11–14%
Pain	67.9	7.1%	75–90	2–5%
Cardiovascular	70.5	-2.5%	70–80	0–3%
Respiratory	54.4	3.4%	60–70	2–5%
Antibiotics and Vaccines	54.4	2.5%	60–70	2–5%
Mental Health	36.8	-5.0%	35–40	(-1)–2%
HIV	24.6	11.5%	35–40	6–9%
Antivirals EX-HIV	33.2	38.1%	35–40	0–3%
All Others	230.2	5.5%	360–415	4–7%

Source: IMS Therapy Prognosis, Sept 2016; QuintilesIMS Institute, Oct 2016
Note: Includes 8 developed and 6 pharmerging countries: U.S., EU5, Japan, Canada, China, Brazil Russia, India, Turkey, Mexico

Comparison of key countries and regions

The U.S. is the leading global market, growing at 6.9% over the past five years and expected to grow by 6–9% over the next five years. China has broadly kept pace with U.S. market growth while no other global market has done so (see Exhibit 3). China became the number two global market in 2012, passing Japan which had been the number two market since 1975 when we began measuring medicine spending in our publication World Review™. China continued to grow at double-digit growth rates until 2015 when it slowed to 5.6% following a series of price cuts. China is expected to grow at a more modest 5–8% rate to 2021 when it will reach $140–170 billion (see Exhibit 4).

Generally over the past decade and forecast for the next five years, developed markets have gradually slid down the rankings of country spending as pharmerging markets have risen. Considering the vastly larger populations in pharmerging markets, where 4 of the world's 7 billion people live, this growth also brings attention to the remaining inequality in access to healthcare globally.

The ten developed markets including U.S., Japan, Germany, U.K. Italy, France, Spain, Canada, South Korea and Australia represent a diverse range of health systems from the way in which they are funded, controlled and their expectations of spending and growth. Japan and France have a range of growth expected from a 1% decline to 2% growth, each with significant government focus on the price, associated volumes and overall spending of innovative medicines. Whereas Japan retrospectively cuts prices every two years—and more sharply if a medicine is more widely used than forecast—France attempts to control spending with reimbursement controls at launch, based on clinical quality assessments, and across-the-board caps on spending which result in paybacks to the government in the case of overspend.

Other developed markets represent generally less aggressive or direct measures in controlling drug spend and as a result will see modestly higher spending growth through 2021. The group of ten developed countries will grow on average by 4–7% to 2021 and represent 67% of global spending in that year—that share down slightly from 68% in 2016.

Exhibit 3: Top 20 Countries Ranking Constant US$

Exhibit	2011	Index	Exhibit	2016	Index	Exhibit	2021	Index
1	U.S.	100	1	U.S.	100	1	U.S.	100
2	Japan	24	2 ▲1	China	26	2	China	25
3 ▲2	China	20	3 ▼1	Japan	19	3	Japan	14
4	Germany	11	4	Germany	10	4	Germany	8
5 ▼2	France	10	5	France	7	5 ▲3	Brazil	6
6	Italy	7	6	Italy	6	6 ▲1	U.K.	6
7	U.K.	6	7	U.K.	6	7 ▼1	Italy	5
8	Spain	6	8 ▲2	Brazil	6	8 ▼3	France	5
9	Canada	5	9 ▼1	Spain	5	9 ▲2	India	5
10 ▲1	Brazil	5	10 ▼1	Canada	4	10 ▼1	Spain	4
11 ▼1	South Korea	3	11 ▲2	India	4	11 ▼1	Canada	4
12	Australia	3	12	Australia	3	12 ▲1	South Korea	2
13 ▲1	India	3	13 ▼2	South Korea	3	13 ▲1	Russia	2
14 ▼1	Mexico	2	14 ▲1	Russia	3	14 ▲2	Turkey	2
15 ▲7	Russia	2	15 ▼1	Mexico	2	15 ▼3	Australia	2
16 ▲3	Poland	2	16 ▲5	Turkey	2	16 ▼1	Mexico	2
17 ▲9	Argentina	2	17 ▼1	Poland	1	17 ▲1	Saudi Arabia	1
18 ▼3	Netherlands	2	18 ▲6	Saudi Arabia	1	18 ▼1	Poland	1
19 ▼3	Belgium	2	19 ▲2	Argentina	1	19	Argentina	1
20 ▼3	Switzerland	2	20	Switzerland	1	20 ▲7	Egypt	1

Source: IMS Market Prognosis, Oct 2016

▼▲ Change in ranking over prior five years

Appendix notes: Rankings based on Constant US$. Argentina based on US$ with variable exchange rates due to hyperinflation. Index reflects comparison to the U.S. of spending in Constant US$.

Ten years ago we first defined pharmerging markets as low income countries with high pharmaceutical growth, set to emerge as strong investment opportunities for multinationals as well as being social development success stories in their own right. At that time there were seven countries which met our criteria (China, Brazil, Russia, India, South Korea, Mexico and Turkey).

Over the past decade that number has grown to 21, and some countries like South Korea have notably "emerged" as developed markets, while others have appeared only for a limited time as long-term growth prospects and sustainable development have remained elusive. Notable for their economic and political challenges in recent years, Ukraine, Venezuela, Romania and Thailand were once counted as pharmerging markets but while they still have per capita incomes below $30,000 on a purchase price parity basis, their economic weakness will prevent them from funding the pharmaceutical spending growth of >$1 billion over the next five years that would result in their inclusion as pharmerging. The latest update of our definition also includes four new countries (Bangladesh, Chile, Kazakhstan and the Philippines) each of which will face their own economic challenges to sustain healthcare investments that over time will provide wider coverage for millions of their people as well as spur more investment and focus from innovators to the diseases their populations face.

Exhibit 4: Key Region and Country Spending and Growth to 2021

	2016 US$Bn	2011–2016 CAGR Constant US$	2021 US$Bn	2016–2021 CAGR Constant US$
Global	**1,104.6**	**6.2%**	**1,455–1,485**	**4–7%**
Developed	**749.3**	**5.4%**	**975–1,005**	**4–7%**
U.S.	461.7	6.9%	645–675	6–9%
EU5	151.8	3.9%	170–200	1–4%
Germany	43.1	4.4%	49–59	2–5%
U.K.	27.0	6.7%	34–38	4–7%
Italy	28.8	5.2%	34–38	1–4%
France	32.1	0.7%	33–37	(-1)–2%
Spain	20.7	3.2%	23–27	1–4%
Japan	90.1	2.0%	90–94	(-1)–2%
Canada	19.3	3.0%	27–31	2–5%
South Korea	13.0	2.9%	14–18	3–6%
Australia	13.5	6.3%	13–16	0–3%
Pharmerging	**242.9**	**10.3%**	**315–345**	**6–9%**
China	116.7	12.4%	140–170	5–8%
Tier 2	55.8	11.4%	75–85	8–11%
Brazil	26.9	11.3%	32–36	7–10%
India	17.4	12.1%	26–30	10–13%
Russia	11.6	10.5%	14–18	5–8%
Tier 3	61.5	6.5%	82–86	6–9%
Rest of World	**112.4**	**3.5%**	**130–160**	**3–6%**

Source: IMS Market Prognosis, Oct 2016

The types of medicines available, and chosen by people around the world are substantially different, with 78% of pharmerging markets spending on products other than the original from the inventors or marketers of a medicine, compared to 69% of developed market spending going to those originators (see Exhibit 5). Developed markets have historically provided and supported patent protection for originators, and followed patent expiry with rapid and significant erosion of those medicines to replace their usage with generics. The development of approval pathways for biosimilars over the past decade along with patent expiries for both small molecules and biologics will offset branded growth and contribute to slower growth in developed markets over the next five years.

Pharmerging markets have only begun to more fully support intellectual property rights in the last decade, and most still retain a significant legacy of use of non-original medicines. The use of these medicines ranges from copy products, to branded non-original products, to over-the-counter medicines (OTC), to a range of traditional Chinese, Indian and Japanese medicines that compete with biopharmaceutical medicines in some markets.

Exhibit 5: Spending and Growth by Region and Product Type

Spending 2021 US$	Original Brands	Non-Original Brands	Unbranded	Other Products	Total US$Bn
Global	56%	22%	12%	10%	$1,455–1,485Bn
Developed	69%	14%	12%	5%	$975–1,005Bn
Pharmerging	22%	42%	14%	22%	$315–345Bn
Rest of World	51%	27%	8%	14%	$130–160Bn

2017–2021 CAGR Constant US$	Original Brands	Non-Original Brands	Unbranded	Other Products	Total
Global	3–6%	9–12%	3–6%	3–6%	4–7%
Developed	3–6%	13–16%	1–4%	0–3%	4–7%
Pharmerging	4–7%	7–10%	8–11%	5–8%	6–9%
Rest of World	2–5%	4–7%	3–6%	3–6%	3–6%

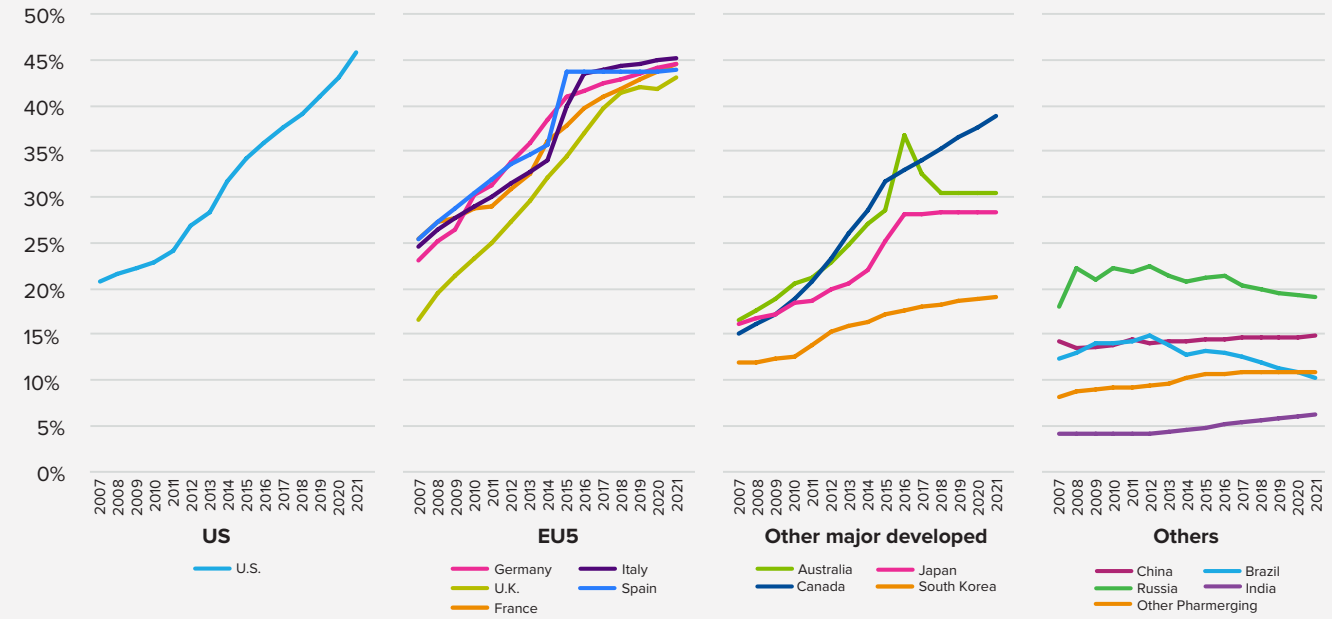
Source: IMS Market Prognosis, Sept 2016; QuintilesIMS Institute, Oct 2016
Notes: Spending Share point values for guidance, Growth estimates +/– 1.5%; Other Products includes OTC products and other non-categorized products

Global medicine spending and growth will be driven by divergent patterns over the next five years. Developed markets will balance a substantial surge in spending on new medicines with cost controls, a focus on pricing and transparency across markets and the impact of patent expiries at $170 billion (1/3rd greater than in the last five years). Pharmerging markets will grow more slowly in dollar terms than in the last five years as China (the largest market and largest growth driver) slows to 5–8% growth from an average 12.4% in the last five years. Pharmerging countries have widely varying economic, social and healthcare environments and while they share a common theme of being driven by lower-cost non-original medicines, they retain significant variations in the mechanisms with which they fund, manage and oversee healthcare and medicines.

Rising specialty medicine use

Innovation in specialty medicines will continue to lift the share of global spending from 30% in 2016 to 35% in 2021 driven by the adoption of new breakthrough medicines. While specialty medicines will continue to increase in share in developed markets, and approach half of medicine spending in the U.S. and EU5, in pharmerging markets specialty medicines will continue with lower share of 5–20% of total medicines spending (see Exhibit 6). Growth of specialty medicines will be constrained by cost and access controls and a greater focus on assessments of value.

Exhibit 6: Specialty Medicines Share of Spending 2007–2021 Constant US$



Source: QuintilesIMS Institute, Oct 2016

In addition to geographic and product-type diversity, countries also demonstrate significant heterogeneity in the ways medicines are priced. Some countries directly manage the price of medicines, negotiating directly with manufacturers at launch, controlling price increases (if any are allowed) and mandating rebates as well as periodic price cuts. Others, like the U.S., devolve price negotiations to markets, and allow and even encourage confidential discounts and rebates, which enable market participants to manage drug costs, but also mask the true nature of medicine spending and price negotiation from observers and the general public. In this report, we continue our efforts to estimate the net spending on medicines to provide some greater transparency and understanding of the underlying trends. We have undertaken these estimates using public sources as well as expert input from countries around the world, but while a majority of global spending is related to publicly traded corporations, a significant proportion is not and the estimates are therefore inherently uncertain. Medicine spending is expected to reach nearly $1.5 trillion by 2021 before adjusting for off-invoice discounts and rebates across a range of countries and products around the world. When adjusted for those price concessions, spending is expected to exceed $1 trillion, 25% lower than non-discounted levels (see Exhibit 7).

Exhibit 7: Global Medicine Spending and Growth Drivers US$Bn

Element	Invoice Spending US$Bn	Net Spending US$Bn	% Difference	Comment
2016 Spending	1,105	868	~ 21%	Medicine spending grew by $148.2Bn over the prior five years Off-invoice discounts and rebates in the U.S. at nearly 30% compared to 17% in Europe and lower in the rest of the world
Growth 2017–2021				
Developed Markets	235			Developed markets overall growth will increase by a third over the $175Bn in the prior five years
Brand Growth	318			Robust flow of new medicines especially in oncology with high value/price levels will drive significant growth
LOE Impact	-170			Brand losses of exclusivity 56% greater in the next five years than the last five years
Generics	87			Generic adoption rates are increasing across developed markets and will account for 31% of spending in developed markets by 2021 up from 28.8% in 2016 and 27.8% in 2011
Pharmerging Markets	110			Growth will slow in pharmerging markets from 10.3% CAGR 2012–16 to 6–9% 2017–21
Other	21			Rest of world projected to grow by $18Bn with forecasted exchange rate effects contributing $3Bn to dollar growth to 2021
Total Growth 2017–2021	367	240	35%	U.S. of gross to net ratio increases by 5% and levels off at ~35% while the rest of the world rebates percentages increase more slowly driven by competition and government price controls
2021 Spending	1,455–1,485	995–1,025	25%	Overall medicine spending will increase nearly 1.5 times faster from 2017–21 than in 2012–16, growing by $367Bn compared to $148.2Bn
2017–2021 CAGR Constant US$	4–7%	3–6%	-1%	Net spending growth will be 1% slower than gross spending growth to 2021

Source: IMS Market Prognosis, Sept 2016; QuintilesIMS Institute, Oct 2016

Notes: Developed markets includes the U.S., EU5, Japan, Canada, South Korea, and Australia; Pharmerging markets include 21 countries which have GDP per capita <$30,000 in 2016 and absolute 5 year forecast growth of >$1Bn from 2017–2021; Other includes rest of world countries and a $3Bn impact of forecast exchange rate changes; LOE denotes the impact on brands from the loss of market exclusivity.

Methodology Note: *This analysis of medicine spending is based on prices reported in QuintilesIMS audits of pharmaceutical spending, which are in general reported at the invoice prices wholesalers charge to their customers including pharmacies and hospitals. In some countries, these prices are exclusive of discounts and rebates paid to governments, private insurers or the specific purchasers. In Other countries, off-invoice discounts are illegal and do not occur. The mix of true prices and opaque pre-discounted prices means the analyses in this report do not reflect the net revenues of pharmaceutical manufacturers. As a part of this report, the QuintilesIMS Institute has compared IMS audited spending data to reported sales, net of discounts, reported by publicly traded companies and made estimates of future off-invoice discounts and rebates. That analysis is shown in the column labeled "Net Spending US$Bn" above.*

Transformations in disease treatments

- New medicines reaching patients will be historically large in number and will address significant unmet needs in cancer, and a new range of diseases not as commonly targeted with immunology treatments including dermatology and respiratory
- New medicines of note include treatments for metabolic conditions, immunology treatments for diseases ranging from dermatology to respiratory and CNS conditions
- In addition to the medicines that we'll see come to the market through 2021, we'll see the evolution of new platforms such as CRISPR, advances in harnessing the gut microbiome to treat diseases, and regenerative cell technologies
- Cancer represents the largest category of new medicines and a range of new mechanisms will continue to revolutionize cancer treatments bringing improved outcomes, longer survival and greater tolerability for patients
- A wide range of existing companies and new participants will bring these cancer products to market over the next five years

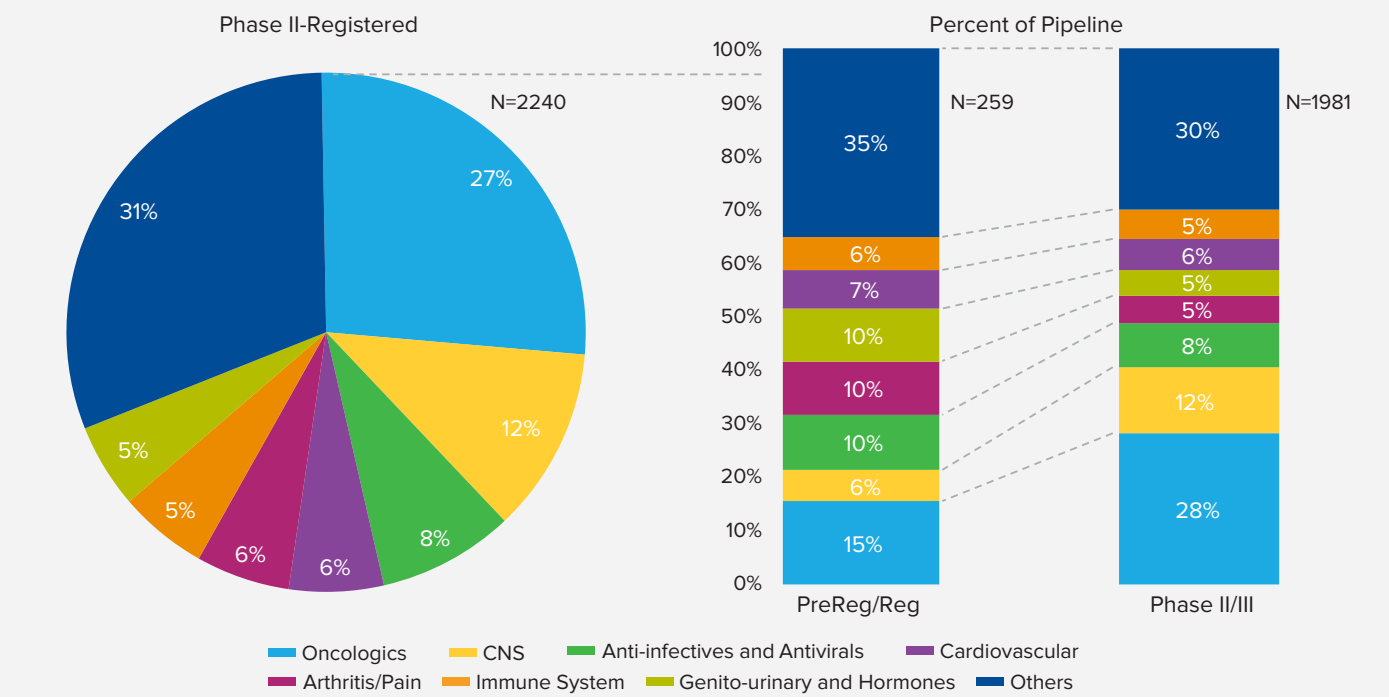
New medicines available in 2021

As key drug classes that serve as standard of care go off patent, an increasing number of diseases are being treated with lower cost options such as generics and biosimilars. However, a new wave of innovation continues to replenish the pipeline and will provide essential therapeutic advances for patients. These will come not only in underserved conditions for smaller patient populations, such as hemophilia and ANCA associated vasculitis , but will also make strides for long-term acquired chronic diseases like Alzheimer's and atherosclerosis that affect large populations and drive cost for the health system. In addition to novel medicines, platform technologies that may transform care across multiple potential disease targets, like CRISPR Cas9 gene editing, regenerative cell therapies, and new approaches to targeting disease through the gut microbiome or replacing blood components with those from healthy individuals will evolve. Though farther out, these platforms too pose exciting new approaches to therapeutics.

Recent successes in cancer therapeutics, encouraged by opportunities for breakthrough therapy designations and shorter development cycles have led over a quarter of the entire late stage pipeline to be focused on the development of oncologics (see Exhibit 8). Therapies for central nervous system (CNS) disorders follow, making up almost an eighth (12%) of the total pipeline. After long delays in bringing drugs for CNS disorders to market—complicated by poor understanding of disease mechanisms and development project failures due to side-effects and lack of efficacy among several of the developmental new classes of therapies—therapies focused on disease modification in Alzheimer's, multiple sclerosis, and even Parkinson's may finally reach the market through 2021.

A wave of new therapies moving through the registration process and soon to come to market include therapies in the anti-infectives and antivirals category —for HIV, bacterial disease, anthrax, hepatitis c, and malaria; therapies in the arthritis and pain category—notably for osteoarthritis and migraine; and Genito-Urinary and Hormones—notably for osteoporosis, hypogonadism, contraception, and infertility.

Exhibit 8: Global Medicines in Late Stage Development in 2016



Source: IMS R&D Focus, Sept 2016; QuintilesIMS Institute, Oct 2016
Note: Drugs included are beyond Phase II development; Cardiovascular includes antihypertensives, anticoagulants, lipid regulators and other cardiovascular therapies; Genito-urinary and Hormones includes women's and men's health, osteoporosis, urological and hormonal therapies. CNS is central nervous system.

New drug classes that will transform care

Many medicines that will transform disease treatment through 2021 will employ novel mechanisms of action to tackle underlying disease processes, or apply a mechanism already shown effective in one disease to another. Improved understanding of the underlying mechanisms of diseases plus a coming of age in the development of immunotherapies and targeted therapies will drive a continued wave of innovation, and address unmet needs across diseases. The most common theme across these areas are an improved understanding of the root causes of inflammation and immune response and the ability to develop and target immunological treatments for new diseases. Exhibit 9 highlights some of the key new mechanisms of action under development and likely to come to market in the 2017–2021 period, and their associated therapy categories.

Biomedical research is often unsuccessful and the examples listed here are understood to be meaningful examples of important progress, accurate as of November 28th, 2016.

Exhibit 9: New Mechanisms of Action Transforming Disease Treatment through 2021 – Part 1

Therapy Category	Disease	MOAs/Technologies	Comment
Immune System Diseases	Psoriasis/ psoriatic arthritis	IL17s marketed but becoming more widely used	Superior efficacy over ustekinumab and anti-TNFs for psoriasis skin clearance and psoriasis plaque resolution and possible improved remission rates for PsA
		Additional medicines targeting IL-23	Possible improved skin clearance vs. adalimumab
		A3 adenosine receptor agonist (A3AR)	Potential similar efficacy to biologics with lower risk of side effects and infection
	RA/ Crohn's/ scleroderma / giant cell arteritis	Additional IL-6 MABs and JAK 1/2 inhibitors	Superior to adalimumab with new indications launching
		A3 adenosine receptor agonist (A3AR)	Oral replacement for MTX
		JAK and (JAK1)-selective inhibitors	May offer efficacy in Crohn's and superior performance in RA vs. tofacitinib along with efficacy in patients with biologic and MTX failures, and proven inhibition of joint damage
	IBD (UC and CD)	SMAD7	Mongersen, down-regulates SMAD7 (messenger RNA) and is delivered directly to the lower digestive tract in a pill with a delayed release coating vs systemic delivery of existing treatments
	Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV)	Oral C5aR inhibitor	Partly blocks cellular binding sites, protecting organs from ANCA, which otherwise bypasses antibody treatments
	Lupus	Interferon alpha receptor inhibition	Lead candidate for Systemic Lupus Erythematosus and lupus nephritis; reduces patients' need for corticosteroids with their associated side-effects
		2nd generation calcineurin inhibitors (CNI)	Possible first oral therapy approved for the treatment of Lupus Nephritis (LN) for add-on to standard of care.
	Ankylosing Spondylitis	IL-17	Possible first drug class besides NSAIDs to prevent radiographic progression in AS
Asthma and Allergy	Atopic dermatitis (AD)	NFκB Decoy Oligonucleotide	Ointment with reduced side effects than existing therapies for with moderate facial symptoms
	Asthma/COPD	IL-5, IL-13, IL-4R inhibitor MABs	Currently only one biologic is available for severe allergic asthma (omalizumab), but a range of new antigen-receptor blockers are in development
Other	Hemophilia	Factor VIII coagulation factor mimetic Bispecific antibody	Superior weekly SQ dosing vs. current SOC 3x per week; Greater than 95% ABR reduction in all cohorts; possible reduced patient resistance

Exhibit 9 continued on the next page...

Exhibit 9: New Mechanisms of Action Transforming Disease Treatment through 2021 – Part 2

Therapy Category	Disease	MOAs/Technologies	Comment
Metabolic	NASH	Numerous mechanisms including PPAR α/δ agonist; FRX; THR-β agonists; Fatty acid bile acid conjugate (FABAC); CCR5 and CCR2 antagonists; LOXL2 mAb, phosphodiesterase 5-lipoxygenase, Pan-caspase protease inhibitor, ACC and ASBT inhibitors; SCD1 inhibitor; Galectin-3 inhibitor	Current treatment options are limited; multiple drugs across many MOAs under development 2019+
	Dyslipidemia	HDL mimetic	Initially for Orphan FPHA may regress atherosclerosis
		Selective PPARα modulator (SPPARMα)	Possible replacement for fenofibrate
		Personalized CETP inhibitor therapy	May reduce CV risk in patients homozygous for the AA genotype ADCY9 gene
		BET inhibitor	For high-risk CVD patients with low HDL
		Antisense apoC-III inhibitor	For high triglycerides
		ATP-citrate lyase inhibitor bempedoic acid	Patients with CV risk factors who cannot tolerate statins due to muscle side effects
		PCSK9 inhibitor MABs (more available)	Patients with CV risk factors with specific genetic markers for response to PCSK9s
	Diabetes	New insulin forms	Insulins - convenient once-weekly and inhaled forms, improved bioactivity and glycemic control
		DPP4s	Once-weekly tablets may improve adherence and reduce burden vs. once-daily meds or multi-drug regimens
		Partial PPAR agonists and selective SSPARMs	May have similar efficacy to TZDs with improved side effect
		Oral, inhaled and once-yearly SC-device GLP-1 agonists	New forms provide convenience
		Glucagon receptor (GCGR) antagonists	May show superiority vs. metformin w/wo sitagliptin but with possible side effects
		G-protein-coupled receptors (GPCR)	May lower glucose levels without an increased risk of hypoglycemia
		SGLT1 and dual SGLT1/SGLT2 inhibitors	Improved glycemic control w/ decreased serum triglycerides, lower BP and weight

Exhibit 9 continued on the next page...

Exhibit 9: New Mechanisms of Action Transforming Disease Treatment through 2021 – Part 3

Therapy Category	Disease	MOAs/Technologies	Comment
CNS	Alzheimer's Disease	Anti-Amyloid β Antibodies/vaccines and immune-targeted therapies	Possibility to affect underlying disease process, reduce Abeta, and reverse symptoms
		BACE Inhibitors	Possible long-term maintenance therapy to limit Aβ production and thereby improve cognitive symptoms and progression
		RAGE receptor blocker	May reduce both Abeta and Tau pathology as well as inflammation and slow cognitive decline
		D2 receptor blocker	For agitation and other behavioral symptoms in patients with Alzheimer's disease
		Metabolic approaches	Address reductions in cerebral glucose utilization an early feature of AD
	Tardive Dyskinesia	VMAT2 inhibitor	Provides relief from the involuntary body movements caused by long term treatment with antipsychotic drugs
	Multiple Sclerosis	Humanized mAb targeting CD20+ B-cells	Active in both RMS and PPMS impacting disease progression; may enable earlier disease treatment
		Additional S1P1R and S1P5Rs / S1P receptor modulators	Reduced disease and disability progression
		Stem cell therapies	Improvements in disability
		Anti-Lingo-1	Direct remyelination of neurons for disease reversal
	Parkinson's Disease	Alpha synuclein targeted therapies including one vaccine vs alpha synuclein; BCR-ABL tyrosine kinase inhibitors	Potentially disease modifying therapies; not just symptomatic therapies
Anti-infectives	HIV	Therapeutic vaccine; Remune, Immune Response BioPharma Vaccine	Induces a HIV-specific T-cell response and work in patients with multi-drug resistance
	Vaccines	Adult vaccines (zoster, HPV, pneumococcus)	Improved efficacy
		Influenza vaccines (recombinant	Faster manufacture, potential for less allergy
	Gram positive bacteria	Pleuromotilins	New class of antibiotic, no cross resistance
	Gram negative bacteria	2nd generation aminoglycosides	Potential to overcome resistance; treat ESKAPE pathogens
	C difficile	Macrocyclic antibiotics; monoclonal antibodies	Potential to overcome resistance
	Fungal infections	Macrocyclic antibiotics; monoclonal antibodies	Potential to overcome resistance
		Dihydrootorate dehydrogenase inhibitor	Efficacy against resistant fungi

Source: IMS R&D Focus , Oct 2016; QuintilesIMS Institute, Nov 2016
Notes: Mechanisms of Actions, Molecules, and Indications are selected examples of areas for the greatest potential growth through 2021; Nonalcoholic Steatohepatitis (NASH); Abbreviations as follows: Familial primary hypo-alpha-lipoproteinemia (FPHA); cardiovascular disease (CVD); Bromodomain and Extraterminal Domain ("BET") proteins; Janus kinase 1 (JAK1); ulcerative colitis (UC) ; apical sodium-dependent bile acid transporter (ASBT) inhibitors; Farnesoid X receptor (FXR); Lysyl Oxidase-Like 2 (LOXL2); primary biliary cholangitis (PBC); peroxisome proliferator-activated receptor (PPAR); Stearoyl Coenzyme A Desaturase 1 (SCD1); amyloid-β (Aβ); Receptor for Advanced Glycation Endproducts (RAGE); Beta-secretase cleaving enzyme (BACE); Standard of Care (SoC); sphingosine-1 receptors (S1P); subcutaneous (SQ); blood pressure (BP); Rheumatoid Arthritis (RA); Psoriatic arthritis (PsA); Inflammatory Bowel Disease (IBD); Ulcerative Colitis (UC); Crohn's Disease(CD); quality of life (QOL); Antineutrophil cytoplasmic antibodies (ANCA)

Immune system disorders

The volume and variety of developments in immunology are consistent with the complexity of the target, but also suggest significant progress has been already been made and will continue. Perhaps the largest catalysts of immunology research historically were the HIV/AIDS epidemic and the battle against cancer,[1] which led to the understanding that improper function of cell processes can have multiple disease outcomes. Some of the earliest discoveries in immunology were therefore originally cancer drugs that found targets in autoimmune/rheumatic disorders like rheumatoid arthritis (RA), psoriasis, psoriatic arthritis, Crohn's disease, ulcerative colitis.

Once targets are identified, translational research seeks to find small molecule or biologic compounds which might act upon it, and clarify their mechanisms of action. The current group of specific drugs in research includes new biologic and small molecule treatments—which may treat the underlying inflammation, progression and damage caused by a number of autoimmune diseases and combat drug resistance—along with expanded indications for existing therapies. In addition, there are reformulations of existing treatments to address tolerability, efficacy or convenience. The number of treatment options will increase rapidly for patients within the autoimmune group of diseases with more than two dozen biologic drugs marketed today and 112 additional new small molecule and biologic medicines in late stage development (see Exhibits 8 and 9).

Within RA, at least one oral candidate, piclidenoson, an A3 adenosine receptor agonist, may be superior in early RA to the first line standard of care, methotrexate (MTX). Additional treatment options to MTX will be extremely helpful to physicians and patients because most patients add biologic treatment to MTX or switch to biologics as a result of failure with MTX, and as many as a third of all patients are intolerant to MTX or discontinue therapy due to side effects. A range of antibody treatments are also already available, in development for additional indications, or still to reach the market. These antibodies generally work to block the reception of various interleukins (cytokines or signaling molecules) either inside or outside the cell, at the receptor site, or by blocking signals intrinsic to the functioning of the immune system. The strategy of blocking cytokines with antibodies has a broad range of disease targets, but the specific targets for a disease depend on the most common cytokines for that disease. For instance, psoriasis, psoriatic arthritis and ankylosing spondylitis have shown important relationship to IL-17 and IL-23 and antibody drugs associated with blocking them are in development. For RA, Crohn's, ulcerative colitis and other related digestive autoimmune diseases, IL-6 antibodies and Janus-like kinase (JAK) inhibitors are providing biologic and small molecule alternatives (respectively) to TNF treatments with more in development. JAK inhibitors work by interrupting the communication of a signal received from a cytokine before it can reach the cell nucleus, thus preventing the immune response, and perhaps without generating resistance. Interestingly, JAK inhibitors seem to function in a helpful way for a range of autoimmune diseases.

Systemic Lupus Erythematosus (SLE), which has been primarily treated with corticosteroids and immunosuppressants to address painful symptoms of the disease, may see the second new drug approved to treat the disease in more than 50 years. Belimumab, launched in 2011, was the first new treatment and works by inhibiting an activation factor (BAFF) for the overactive B-cells in lupus, while a promising new antibody in phase III (anifrolumab), inhibits interferon alpha reception, and reduces patients' need for corticosteroids with their associated side-effects. For the related disease, Lupus Nephritis (LN), the standard of care has been corticosteroids and immunosuppressants, but only 10% of patients typically achieve remission with that approach. Some positive phase II results suggest that an improved immunosuppressant, a 2nd generation calcineurin inhibitor (CNI) voclosporin, could potentially bring fewer side-effects and improved symptom management as part of a corticosteroid-based regimen.

Other immune systems disorders that will see advances include ANCA (Antineutrophil cytoplasmic antibodies) associated vasculitis (AAV) and digestive diseases such as ulcerative colitis, Crohn's disease, and irritable bowel syndrome (IBD). AAV, which harms almost all of the major organ systems of the body including the kidneys, blood vessels, nervous system, heart and lungs is being targeted using a complex method of signal interruption, using new oral C5aR inhibitors, that may provide some protection to organs. The digestive diseases could see a range of transformative drugs. For Crohn's one important developmental drug is mongersen, which down-regulates SMAD7 messenger RNA that triggers immune response. For patients suffering from this disease, the phase II results for the pill with a timed-release coating, which delivers it's small molecule drug directly to the lower intestinal area, suggest a substantially better treatment option could be available in the next five years.

The challenge with all immunology treatments is the inherent complexity of the immune system itself. Most treatments seek to have as narrow an effect as possible, lest they create a cascade of side effects. To date all of the mechanisms in research are imperfect, but researchers are rapidly gaining significant understanding of a range of cell processes, disease pathways and the effects (both positive and negative) of hundreds of compounds, as evidenced by the burgeoning pipeline of immunology treatments for autoimmune disorders. Significantly, approaches to immunology are increasingly finding that some biologic and small molecule drugs have multiple disease targets and progress in one immune disease may translate to progress across many diseases as we gain deeper understanding of the complexity of the immune system. Immunology research will bring significant benefits to the whole range of autoimmune disorders which are the current research targets but also to a range of diseases not previously thought of as related to the immune system.

Metabolic

NASH

One of the more interesting developments in the metabolic area, has been development efforts aimed at an unaddressed aspect of metabolic syndrome—namely the involvement of the liver, which may show cellular changes in fat storage (steatosis) and lead to fatty liver disease, or nonalcoholic steatohepatitis (NASH). It may also lead to liver inflammation and progressive damage, and ultimately cirrhosis. To date there has been little in the way of treatments for NASH despite a sizeable but under-recognized prevalence, with as many as 20–40% of non-alcoholic individuals with type 2 diabetes mellitus (T2DM) also having NASH.[2,3] Because of the link to type 2 diabetes mellitus (T2DM, as well as to other metabolic disorders such as obesity, dyslipidaemia and hypertension) the rise of T2DM and obesity in Asian and Western populations will also increase the levels of NASH. To date, both the lack of existing treatments and the fact that diagnosis requires invasive biopsy have contributed to under recognition of the condition, since even if doctors did diagnose there has been little to do. Medicines with an acceptable risk/benefit ratio for NASH have yet to come to market, however, a range of therapies are expected through 2021, tackling the disease using numerous mechanisms. The first to come to market are likely obeticholic acid, a FRX agonist, and elafibranor, a PPAR α/δ agonist (see Exhibit 9).

Dyslipidemia and cardiovascular disease

Cardiovascular diseases result in heart disease, stroke and death for millions each year. For the last three decades, research identifying the link between high cholesterol, arterial plaque, and adverse cardiovascular outcomes have ultimately led to the widespread use of statins and dramatic reduction in mortality. As research involving lipid fractions (e.g. HDL-C, LDL-C) and lipoproteins has continued, discovery of new mechanisms has resulted in new and even more effective treatment options. Recent developments with PCSK9 inhibitors now enable LDL-C (bad cholesterol) levels to be pushed very low, with evolocumab in combination with a statin, for instance, lowering LDL-C up to 77% more than a

statin alone.[4] The long-term benefits of these treatments remain to be proven, still, additional PCSK9 inhibitors are under development and continue to find their place in the standard of care worldwide, such as among statin intolerant patients.

A number of new therapy classes are also under development in dyslipidemia, with expected benefits in atherosclerosis, and cardiovascular risk. Despite failures of HDL-raising approaches with CETP inhibitors torcetrapib, dalcetrapib and evacetrapib that failed in Phase III trials, HDL-focused therapies continue to be researched. Individual therapies, such as an HDL mimetic therapy (CER 001) initially for the orphan disease Familial Primary HypoalphAlipoproteinemia (FPHA) is expected to regress atherosclerosis by raising HDL in patients with Acute Coronary Syndrome (ACS) patients by promoting reverse lipid transport (RLT). Research on the failed CETP inhibitor dalcetrapib has also resumed, this time with a personalized medicine approach that narrows treatment to patients homozygous for the AA genotype ADCY9 gene and may yield differing results based on substudy findings indicating reduced CV risk.

Other therapies include pemafibrate, a selective PPARα modulator (SPPARMα) on the horizon as a possible replacement for fenofibrate with 3x the potency and greater PPARα selectivity;[5] apabetalone, a BET bromodomain inhibitor, shown to raise ApoA-I and HDL, and thus initially for high-risk CVD patients with low HDL; and an antisense apoC-III inhibitor, volanesorsen, to combat high triglycerides. Finally bempedoic acid inhibits ATP-citrate lyase, an enzyme involved in the cholesterol biosynthesis pathway, may be effective for patients with CV risk factors who cannot tolerate statins due to muscle side effects.

Diabetes Mellitus

The International Diabetes Federation reports that 415 million people currently have diabetes worldwide in 2015, with this number expected to rise to 642 million by 2040.[6] With variable patient response to therapies, there is no one right way to manage diabetes, and the next five years will see a continued flow of new options to meet the varying needs of diabetics. For T2DM patients, new therapy approaches are generating less excitement than those introduced in the last decade, although additional GLP-1, SGLT-2 and , dipeptidyl peptidase (DPP)-4 inhibitors will continue to be approved, as will additional combinations and convenient forms across classes, and new classes continue to be researched.

Type 1 Diabetic Mellitus (T1DM) patients may see more improvements in therapy. Although already on the market, insulins continue to be developed with new delivery forms and mechanisms for varying speed of absorption, and these remain critical to type 1 patients. These include oral, inhaled, once-daily and once-weekly injections. Oral insulins claim to be closer to natural physiological processes of liver absorption, yielding smoother glucose release. Inhaled forms which offer needle-free administration, thought to be an attractive feature to patients, have thus far fared poorly in the market with the withdrawal of Pfizer's Exubera in 2007 and Mannkind's Afrezza failure to gain wide usage since its launch in 2015. Additional developments include long acting forms (such as LY2605541, a once-daily pegylated insulin Lispro) and ultra-long acting once-weekly forms (such as the basal insulins HM12460A and LA1287 under development) that will improve patient convenience; fast-acting forms (BIOD-123); and absorption promoters (such as rHuPH20 a recombinant human hyaluronidase) that can be added to insulins for faster and more consistent absorption. Farther out in phase I, from 6-10 years to potential approval, are uses of drugs with the SGLT-2, DPP-4 and GLP-1 mechanisms for type 1 diabetics, and smart "glucose-responsive insulins" that become active in the body only when needed to improve bioactivity and glycemic control (such as MK-2640).

Autoimmune approaches are also being tried in T1DM—for instance with ustekinumab, an immune suppressant mAb now in Phase II trials —to counter the destruction of pancreatic beta-cells as part of an immune response. Such therapies could be protective of the pancreas, however the immunology approaches are not well targeted and they suppress the entire immune system. Additional basic research is still needed to allow development of medicines targeted to the auto-immune processes of diabetes.

Finally, the utilization of technology, including sensors and apps, will continue to transform care in diabetes, allowing both greater convenience and more active patient management of lifestyle so critical for moving patients along the "path to optimal adherence and persistence" that comes from effective patient activation.[7] For type 1 patients, instead of testing 3-4 times a day, an increasing number of patients in developed markets will use continuous glucose sensors (CGM), that provide continuous data from a chip implanted under the skin, an when paired with an insulin pump which releases insulin as needed, will help manage patients' disease and even encourage positive behavioral changes. For both type 1 and type 2 patients, digital technologies such as food diary apps, fitness trackers, CGM, paired with new drug options continue to advance the quality of life and the adherence of diabetics in developed markets. In the developing world, the cost of newer drug classes, technologies and healthcare infrastructure represent a continued barrier to better treating millions of diabetics.

Central nervous system disorders

Alzheimer's

As the global population ages, the patient population with Alzheimer's is expected to grow rapidly, doubling every 20 years. The current population of 46.8 million patients (estimated worldwide in 2015) is expected to reach 74.7 million in 2030 and 131.5 million in 2050.[8] While the need is clearly large and the systemic costs loom over future healthcare spending decisions, research progress has been frustratingly absent. Very few new therapies for Alzheimer's have reached the market in the past 15 years, and there have been a series of high profile failures. Medicines available to date have only addressed the symptoms of the disease including confusion, memory loss and behavioral symptoms, however research has focused in recent years on disease-modifying agents. Some long-term research projects are reaching their final stages, and promising new approaches that may impact the progression of the disease could still emerge. Perhaps the most challenging aspect of developing treatments is the need to target mild to moderate patients where the measurable effects of the disease (or the treatment) are negligible, and clinical trials must proceed for many years to show an impact. Diagnostics to improve identification of early Alzheimer's continue to progress and will aid drug development by making these minor differences more visible to researchers. Leading approaches target beta amyloid and tau proteins that respectively form the amyloid plaques and neurofibrillary tangles in the brain that characterize the disease, though other approaches target inflammation, and metabolic changes such as insulin-resistance.

A wide range of molecules target Amyloid beta (Aβ or Abeta), the main component of the amyloid plaques. Some strategies attempt to reduce the amount of Abeta produced, such as BACE inhibitors. These include verubecestat, AZD3293/ (a.k.a. lanabecestat), which received fast track designation and has been shown to reduce levels of amyloid beta in the cerebro-spinal fluid, JNJ-54861911 and CNP520. These therapies are seen as a possible long-term maintenance treatments to limit Aβ production and thereby improve both cognitive symptoms and slow the progression of the disease. The hope is that these therapies will have fewer detrimental side effects than seen with earlier BACE1 blockers, such as reduced nerve myelination, neurodegeneration, glucose imbalance, and liver toxicity.

Other anti-amyloid approaches include immune therapies or antibodies against Abeta. Despite Phase III failures of such antibodies as solanezumab and bapineuzumab, similar drugs continue to be developed, with Roche developing crenezumab and gantenerumab—the latter which failed an earlier trial in early presymptomatic patients, but will now be tested with higher doses of the drug and in trials for patients with autosomal-dominant Alzheimer's disease (Alzheimer's genes APP, presenilin-1, and presenilin-2). Another IgG1 monoclonal antibody against a conformational epitope found on Aβ, aducanumab from Biogen also has shown indication it reduces Abeta and also received fast track designation. Finally a RAGE receptor blocker azeliragon, which mediates Abeta transport and accumulation in brain, may reduce both Abeta and Tau pathology as well as inflammation and slow cognitive decline.

Although approaches targeting Tau are also expected to slow progression of the disease, and Tau vaccines are under development, current late stage tau approaches are fewer and include masitinib (AB Science), an oral therapy that targets Tau through Fyn inhibition and TRx0237 (TauRx Therapeutics) and oral, second-generation tau protein aggregation inhibitor. Although TRx0237 failed to slow cognitive or functional decline in people with mild to moderate AD in a recent Phase 3 clinical trial, having seen better results with the drug in monotherapy patients the company intends to modify a second completed AD trial to make it a monotherapy analysis.

Other molecular pathways are also being tried. Brexpiprazole and Aripiprazole, dopamine D2 receptor blockers, may additionally offer some relief of agitation, aggression and other behavioral symptoms in patients with Alzheimer's disease. Other metabolic approaches such as AC-1202 medical food product (caprylic triglyceride), address regional reductions in cerebral glucose utilization—an early feature of Alzheimer's disease— and will compare patient outcomes in ApoE4 carriers vs. non-carriers.

Multiple sclerosis

In multiple sclerosis (MS) too, therapies under development are targeting disease modification, or ways to hinder the disease process rather than symptomatic therapies. A key drug launch expected in the near term is for ocrelizumab (Genentech), a Humanized mAb targeting CD20+ B-cells that has gained designation as a breakthrough therapy having shown evidence of impacting disease progression and efficacy in both relapsing-remitting MS (RRMS) and primary progressive MS (PPMS). It may therefore enable earlier disease treatment. Although Rituxan, an approved CD20 used previously in cancer and RA, also has shown success in progressive MS in early clinical trials, only ocrelizumab is likely to be approved for the condition.

Companies are also increasingly targeting progressive MS more. New S1P1R and S1P5Rs modulators, similar to fingolimod (Gilenya) are being studied in progressive MS, including laquinimod, ozanimod, ponesimod, siponimod, and amiselimod. In a recent Phase III trial, siponimod reduced the progression of disability among secondary progressive MS (SPMS) patients by 21 percent versus placebo.[9] Although the first of the T-cell immunotherapy approaches to MS, Tcelna, recently failed in a Phase IIb study, cell therapies are also likely to continue to be developed in the MS space, in addition to cancers. Finally, one of the more exciting approaches to MS is to directly reverse the de-myelination of neurons—the hallmark and underlying cause of the disease. At least one re-myelinating agent, the anti-Lingo monoclonal antibody opicinumab, is under development, and aims to promote the development of oligodendrocytes that repair the damaged myelin. Although the drug failed to improve disability or slow progression in recent Phase II trial, Biogen continues to develop it.

Parkinson's disease

Within Parkinson's disease (PD), the class generating the most excitement as potential disease modification products are targeted against Alpha synuclein (aSyn)—a protein that plays a key role in disease onset and progression— including two vaccines: Affitope PD03A for treating early PD, and a boost immunization Affitope PD01A with antibodies that bind to fibrilic aSyn. Borrowing from the cancer playbook, tyrosine kinase inhibition, used to arrest tumor growth, is also being investigated to promote survival of neurons in neurodegenerative disease. In Parkinson's, BCR-ABL tyrosine kinase inhibitors—which are used in CML and approved by FDA (e.g. nilotinib, bosutinib etc.)—may have a protective role, where there has been some suggestion that c-ABL may be dysfunctional.

Anti-infectives and antivirals

Antivirals

Perhaps having seen the greatest impact on therapy in the past few years, Hepatitis C will continue to see treatments for additional genotypes and with shorter durations. However, the impact on treatment will now be much less transformative, with much of the population well served with current options. Still over 170mn people remain globally with the disease[10] and it will be decades before they can all be treated. HIV vaccines—long sought after—may reach the market in the next few years but the most advanced effort, Immune Response BioPharma's HIV Vaccine, received a complete response letter for application deficiencies from the U.S. Food and Drug Administration (FDA) in February of 2016. The vaccine's trial data suggested an HIV-specific T-cell response and efficacy in patients with multi-drug resistance, suggestive of an exciting vaccine development if it can overcome the doubts of regulators. Other expected advances in viral vaccines include faster manufacturing and reduced potential for allergy with the influenza virus vaccines (recombinant), and improved efficacy for adult vaccines for zoster, human papilloma virus (HPV) and pneumococcus. Finally, with much public attention on Zika virus, there are at least 11 projects now focused on the development of Zika virus vaccines. Although unlikely to hit prior to 2021, two of these are in Phase I clinical trials, including one DNA, and one mRNA vaccine, and another inactivated virus vaccine Phase I trial expected early next year.

Antibiotics and antifungals

The development of new antibiotic and antifungal treatments is complicated by the growing resistance to existing treatments. New classes are essential, and one new class of antibiotics, pleuromotilins, has shown no cross resistance for the treatment of gram positive bacteria. For the treatment of gram negative bacteria, second generation aminoglycosides are the most promising with the potential to overcome resistance and treat the six key ESKAPE pathogens that show growing multidrug resistant virulence. Macrocyclic antibiotics and monoclonal antibodies are also under development to treat C difficile, while the new class of dihydrootorate dehydrogenase inhibitors and oral formulations of encochleated amphotericin are expected to be effective against resistant fungal infections (see Exhibit 9).

Asthma and Allergy

Atopic dermatitis

Atopic dermatitis is an inflammatory autoimmune disease that to date has been treated as a symptomatic dermatological condition characterized by itching and lesions. A range of small molecule and biologic medicines are now in late stage development that begin to treat the underlying inflammation and progressive nature of the disease, potentially offering

sustained relief for patients. One therapy, NFκB Decoy Oligonucleotide, is a short artificial nucleic-acid that inhibits gene expression of the protein NF-kappa B and is expected to have fewer side effects for patients with moderate facial symptoms as a topical ointment as compared with currently used topical corticosteroids and other creams and topical treatments. Other treatments under development include PDE4 inhibitors, such as crisaborole (Eucrysa) and apremilast (Otezla), in both topical and oral forms, and mAbs targeting IL-4R and IL-13 such as dupilumab, tralokinumab and lebrikizumab, which are subcutaneous therapies administered every 2 or 4 weeks.

Other Diseases

A number of other diseases across therapy areas will also see advances. While less than 1 million people suffer from hemophilia A or B globally, they are among some of the most costly patients to treat because of frequent transfusions, costly medicines and often have a poor health prognosis, particularly in the absence of treatment. New versions of a variety of clotting factor drugs are in development, including emicizumab (ACE910, Chugai Pharmaceuticals/Genentech) that mimics the cofactor function of factor VIII. Many of these will decrease the rate of bleeding events while improving the convenience of therapy for patients and healthcare providers. Additionally, the market will see a number of drugs launched for orphan diseases. In tardive dyskinesia, for instance, where there is no current FDA approved treatment, the VMAT2 inhibitor valbenazine show promise as a once-daily treatment, superior to tetrabenazine (currently the standard of care) which is rapidly metabolized and must be administered frequently throughout the day.

Beyond 2021

In addition to the medicines that will come to the market through 2021, we'll see the evolution of new platforms such as CRISPR, advances in applying the microbiome to diseases, and regenerative technologies.

Regenerative cell therapies including stem cells: Although the only stem cell treatment widely approved and used globally consists of versions of bone marrow/hematopoietic stem cell transplantation in certain cancers. Other regenerative cell therapies are under development. These include in therapy areas as diverse as cardiology, central CNS disorders (MS, Parkinson's, amyotrophic lateral sclerosis/ALS, and others), arthritis, inflammation, asthma, metabolic disorders (diabetes) and liver disease.

Blood components including IVIG, albumin, Alpha-1 Antitrypsin: Applications include CNS disorders (including Alzheimers, ALS); cirrhosis; cystic fibrosis and diabetes

Microbiome: Approaches to adjusting the human gut microbiome—the many strains of microbes that live in the GI tract—offer new and potentially lower cost options for otherwise complex diseases, such as autoimmune disorders (e.g. Lupus, RA as well as GI ones IBS, UC, Crohn), metabolic disorders such as type 2 diabetes and obesity, and infectious diseases like (C.difficile)

CRISPR–Cas9: This simple and rapid approach to gene editing has generated widespread excitement and gained notoriety as a tool to treat rare diseases with single gene defects, including Muscular Dystrophy. Although complicated by ethical questions (i.e. eugenics that might be enabled by this technology), CRISPR is moving ahead in areas of personalized and targeted medicine. The first CRISPR clinical trial to move ahead in the U.S. will help augment T-cell cancer therapies, using the gene editing process to make edits to patient's T-cells that allow them to detect and target cancer cells, remove a protein that could slow this process, and prevent the cancer cells from disabling them.[11] Other gene editing techniques are also being tried such as zinc-finger nuclease and TALENS. Not surprisingly, the majority of these platform technologies are being explored first in Oncology.

Oncology

Cancer remains among the leading causes of morbidity and mortality globally with over 14 million new cases each year and 8 million resultant deaths each year, rising by about 70% through 2022 to 22 million.[12] New medicines have had a significant impact on the treatment of cancer in recent years, with treatments slowly becoming more sophisticated, tailored to specific tumor types, providing personalized treatments to patients, and beginning to harness not only the body's molecular pathways, but also elements of the immune system (see Exhibit 10). Such immunotherapies harness elements of the patient's own immune system to treat cancer, with some treatments sensitizing and increasing immune response to specific targets or tumors, some altering immune cells and antibodies outright to take aim at the disease and others engineering antibodies or immune system proteins. The key developments in oncology through 2021 will likely come from continued introduction of these immunotherapies to the market, and the broadening of immunotherapy strategies to more combination regimens and further indication targets. Also, due to their ability to increase a patient's ability to fight cancers broadly, immunotherapies are expected to add on to existing regimens and provide extended survival as shown in clinical trials.

Immune checkpoint inhibitors

A notable immune oncology approach with very promising results employs checkpoint inhibitors,[13] monoclonal antibodies (mAbs) that are already in use to unleash the body's own immune system. In a normal functioning body checkpoint molecules on immune cells are regulated to ensure these cells attack only foreign pathogens. Although cancers may hinder this process and evade attack by switching off or inhibiting checkpoints, this frees immune cells to become active against cancers. Recent immune checkpoint inhibitors such as anti CTLA4 and PD-1 will continue to be a key molecular target for immune activation in the next 5 years, having proven success with ipilumumab, nivolumab and pembrolizumab and showing robust clinical response. Both of these mechanisms, and new immune checkpoint inhibitor strategies (see Exhibit 10) have strong potential to grow the market in the next 5 years.

The use of single therapies currently is also likely to give way to use of immunotherapy combinations including multiple checkpoint inhibitors in combination over time, in line with nivolumab (Opdivo) plus ipilimumab (Yervoy)—the first immunotherapy combination for metastatic melanoma. For instance, being studied in PIII are the IDO1 inhibitor epacadostat in combination with anti-PD-1 therapy pembrolizumab as first-line treatment for patients with advanced or metastatic melanoma; and two immune checkpoint inhibitors, durvalumab and tremelimumab are being combined in clinical testing across a range of cancers (including gastric cancer; pancreatic ductal carcinoma; NSCLC; SCCHN; bladder). Additionally for NSCLC, at least two combinations are being tried: Anti PD-LI atezolizumab (Tecentriq) plus nivolumab and platinum-based doublet chemotherapy; and a PD-1 combination including pemetrexed, pembrolizumab (Keytruda) and carboplatin.

Cell therapies

Generally created through harvesting, culturing or specific gene-editing techniques, cell therapies are a general term for a range of personalized medicine approaches being explored first in cancer and with potential targets in many diseases. Cells collected from a patient or other biological host must subsequently go through complex manufacturing processes to avoid immune responses, and the associated practical delay may act as a practical hindrance to their adoption in the market. This was the case with Sipuleucel-T (Provenge) which cultures a patient's own prostate cancer cells to create an anti-cancer cell therapy unique to that patient. There may be some similar market resistance to adoption of some Chimeric antigen receptor T-cell (CAR-T) therapies as some require a 2-week patient-individualized manufacturing

process. The key factor in adoption will likely be directly linked to the associated improvement in outcomes as compared to other treatment options. A number of major companies are researching in this area including Novartis, Juno, Kite (with Amgen, Bluebird Bio and Genentech) and Cellectis (with Servier/Pfizer). The Cellectis product is unique in that it offers an off-the-shelf allogenic cell product that reportedly avoids immune incompatibility. Most of the early cell therapies are modifying T-cells to target immune antigens for several leukemias including chronic lymphocytic leukemia (CLL) and acute lymphoblastic leukemia (ALL). Cell therapies require the modification of healthy immune cells to target cancerous cells and while this approach can be widely applied, it is generally limited to cases where a specific antigen can be identified on the target cancer cells.

Exhibit 10: Oncology Immunotherapies and Molecular Targeted Drugs Expected to Drive Pipeline Growth

Mechanism of Action	Molecules	Indications
Immune checkpoint inhibitors		
More PD-1 and anti-CTLA4 antibodies	pidilizumab, MK-3475, MEDI4736, tremelimumab	Melanoma, NSCLC, mCRC, DLBCL, bladder
NEW immune checkpoint inhibitors targeting OX40, TIM-3, ICOS, BTLA, CD40, CD27, LAG-3, 4-1BB, GITR, PD-L1	CP-870,893, varlilumab, BMS-986016, urelumab, PF-2566, TRX518, MK-4166, durvalumab	Many if not all types of cancer
Immuno-oncology combinations	IDO1 inhibitors plus anti-PD-1 Anti PD-L1 plus anti-CTLA-4 Anti PD-L1 plus other targeted therapies Anti PD-L1 plus MEK inhibitor	Solid tumors, gastric cancer, pancreatic ductal carcinoma, NSCLC, SCCHN, bladder, Microsatellite instability–high CRC
Cell therapies CAR-T, T-cell therapy, cancer stem cells	CTL019, UCART19,KTE-C19, JCAR017	ALL, CLL, B-cell malignancies, DLBCL, TFL, PMBCL, MCL, solid tumors
Other Immunotherapy strategies Oncolytic viruses, treatment vaccines, bispecific antibodies, T Cell Receptors, Immunostimulants and immunomodulators, Toll Like Receptors	Viruses: NV1020, MV-NIS, Reolysin, PVS-RIPO, dozens more. Vaccines: ProscaVax, GVAX, NeuVax, CG0070, dozens others Bispecific Abs: Blinocy, catumaxomab, ertumaxomab, FBTA05, many others	Many solid tumor types
Molecular targeted agents ***Targets:*** FGFR2, ROCK, TRK, Notch, Hedgehog, ALK, ROS, BRAFV600E, cMET, SMO, JAK, PARP, CDK4/6, BRCA, PI3K, T790M, BH3	(Hundreds), many in combination with genetic testing and companion diagnostics	Targets based on specific molecular target present in specific tumor types, enables personalized medicine and treatment approaches
ALK inhibitors	ensartinib, dalantercept, TSR 011, entrectinib, lorlatinib	NSCLC, Solid tumors, Advanced RCC, Lymphomas
MEK inhibitors	binimetinib (Array Pharma), selumetinib	Melanoma and CRC, other solid tumors, Thyroid Cancer and NF1
PARP or similar DNA damage response inhibitors	veliparib, niraparib, rucaparib, olaparib.	Ovarian cancer and maintenance, advanced squamous NSCLC, other solid tumors
Cyclin-Dependent Kinase (CDK) 4/6 Inhibitors	ribociclib, roniciclib, dinaciclib, abemaciclib	Breast, NSCLC, Melanoma, SCLC, CLL
BH3-mimetics/Bcl-2 inhibitors (pro-apoptosis)	venetoclax, obatoclax	CLL, SCLC, leukemia, lymphoma, myelofibrosis, mastocytosis.
Antibody drug conjugates (ADCs and ADCCs)	inotuzumab ozogamicin, mirvetuximab soravtansine, depatuxizumab mafodotin, vadastuximab talirine	Glioblastoma, ALL, AML, myelodysplastic syndrome, SCC, fallopian tube, ovarian, peritoneal, endometrial, many solid tumors CLL, NHL, RCC, DLBCL

Source: IMS R&D Focus, Oct 2016; QuintilesIMS Institute, Nov 2016

See table notes and definitions on the next page.

Exhibit 10: Table Notes (Definitions)

Term	Definition	Term	Definition	Term	Definition
4-1BB	TNF receptor-related T cell antigen	FGFR2	Fibroblast growth factor receptor 2	PD-1	Programmed cell death protein 1
ADCC	Antibody dependent cell-mediated cytotoxicity	GITR	Glucocorticoid-induced TNFR-related protein	PD-L1	Programmed death-ligand 1
ADCs	Antibody drug conjugates	Hedgehog	Intercellular signaling protein involved in body plan development and cell differentiation	PI3K	Phosphoinositide-3-kinase
ALK	Anaplastic Lymphoma kinase protein	ICOS	Inducible T-cell COStimulator	PMBCL	Primary mediastinal B-cell lymphoma
ALL	Acute lymphoblastic leukemia	JAK	Janus kinase; involved in cytokine signaling	RCC	Renal cell carcinoma
BRAF V600E	Mutation of the BRAF gene	LAG-3	Lymphocyte-activation gene 3	ROCK	Rho-associated, coiled-coil-containing protein kinase
BRCA	tumor suppressor gene mutation that produces breast-ovarian cancers	MCL	Mantle cell lymphoma	ROS	Proto-oncogene tyrosine-protein kinase ROS
BTLA	B- and T-lymphocyte attenuator	mCRC	Metastatic Colorectal Cancer	SCC	Squamous cell carcinoma
CAR-T	Chimeric antigen receptor T-cell therapy	MEK	Mitogen-activated protein kinase	SCCHN	Squamous Cell Carcinoma of the Head and Neck
CD	Cluster of differentiation - a protocol for identification of cell surface targets	NF1	Neurofibromatosis Type 1	SCLC	Small-cell Lung Cancer
CDK	Cyclin-dependent kinase	NHL	Non-Hodgkin lymphoma	SMO	Smoothened receptor; hedgehog pathway
CLL	Chronic Lymphocytic Leukemia	Notch	Signaling pathway involved in many cancers	TFL	Follicular Lymphoma
cMET	Tyrosine kinase encoded by the MET gene	NSAA	Non-steroidal antiandrogen	TIM-3	T-cell immunoglobulin and mucin-domain containing-3
CRC	Colorectal cancer	NSCLC	Non-small Cell Lung Cancer	TRK	Tropomyosin receptor kinase
CTLA-4	Anti-cytotoxic T-lymphocyte antigen 4	OX40	Tumor necrosis factor receptor 4 (TNFRSF4)		
DLBCL	Diffuse Large B-cell Lymphoma	PARP	Poly ADP ribose polymerase (inhibitors)		

The most ground-breaking areas of cancer research are in the area of cancer stem cells. Cancer stem cells (CSCs), similar to non-cancerous stem cells, are thought to be key to the creation of many new types of cells. Research has confirmed the presence of CSCs in multiple tumor types,[14] indicated in some way by the variety of distinct types of cancer cells within the same tumor sample. By identifying cancer stem cells and then testing treatments on those progenitor cells, more specific and effective treatments may be developed to prevent relapse and metastases across a range of tumors. In this way, CSCs are indicative that researchers are not fighting a disease but rogue cell processes, and success is more likely to be found at the root cause than by fighting the downstream expression of aberrant cell behaviors.

Other immunotherapy approaches continue to be developed but have yet to progress to the market to date. These include the use of viruses to insert anticancer DNA into affected cells, therapeutic vaccines, immunostimulants and immunomodulators as well as bispecific antibodies (engineered proteins containing parts of two antibodies enabling targeting of two antigens) that simultaneously bind to cytotoxic cells and cancerous cells.

Molecular targets

Outside of immuno-oncology, therapies against hundreds of molecular targets continue to be developed—many as personalized medicines in combination with genetic testing and companion diagnostics that look for specific molecular targets present in specific tumor types and then treat them by altering biological pathways. These include a wide range of targets (see Exhibit 10). Among these, next generation therapies of ALK inhibitors will address crizotinib resistance and will become the standard of care in the next 5 years, while Third Generation EGFR TKIs against the T790M mutation, which have recently begun to be launched to the market beginning with osimertinib (Tagriisso) for T790M mutation positive non-small cell lung cancer, will also combat drug resistance to first- or second-generation TKIs. Other therapies in this class are also being developed including rociletinib HM61713, ASP8237, EGF816, and PF-06747775.

MEK inhibitors (binimetinib, selumetinib) continue to be developed for melanoma, colorectal and thyroid cancers, and neurofibromatosis type 1. Combined with Anti PD-L1, they are expected to strengthen the effect of Microsatellite stable CRC since MEK inhibition may make a tumor more responsive to immunotherapy.

PARP or similar DNA damage response inhibitors including veliparib (Abbvie), being developed for advanced squamous NSCLC, and niraparib (Tesaro) and rucaparib (Clovis), which are being developed for ovarian cancer maintenance. AstraZeneca's marketed PARP inhibitor olaparib (Lynparza) continues to be developed for additional indications including BRCA1/2 or ATM gene mutated metastatic castration resistant prostate cancer.

In the late-stage pipeline, CDK inhibitors, which inhibit cancer cell proliferation, are thought to be promising as most cancer cells demonstrate CDK mutations. Existing treatments such as palbociclib (Ibrance) for ER-positive and HER2-negative breast cancer will continue to be researched for additional uses and a number of other CDK4/6 inhibitors continue to be developed.

Apoptosis, or cell-death, generally doesn't occur in cancer cells but some molecular targeting approaches are attempting to induce apoptosis in elusive cancer cells using BH3-mimetics and Bcl-2 inhibitors. Some challenges have appeared in trials which may be because treatments are too effective and result in tumor lysis syndrome (TLS). TLS can occur from a range of cancer treatments as an overflow of destroyed tumor cells collect in the kidneys and the body struggles to excrete them rapidly enough, potentially resulting in kidney failure or even death. Apoptosis-inducing approaches are in development for a in a range of solid tumors and leukemias and could prove very valuable additions to treatment, if they can be made to be both effective and tolerable.

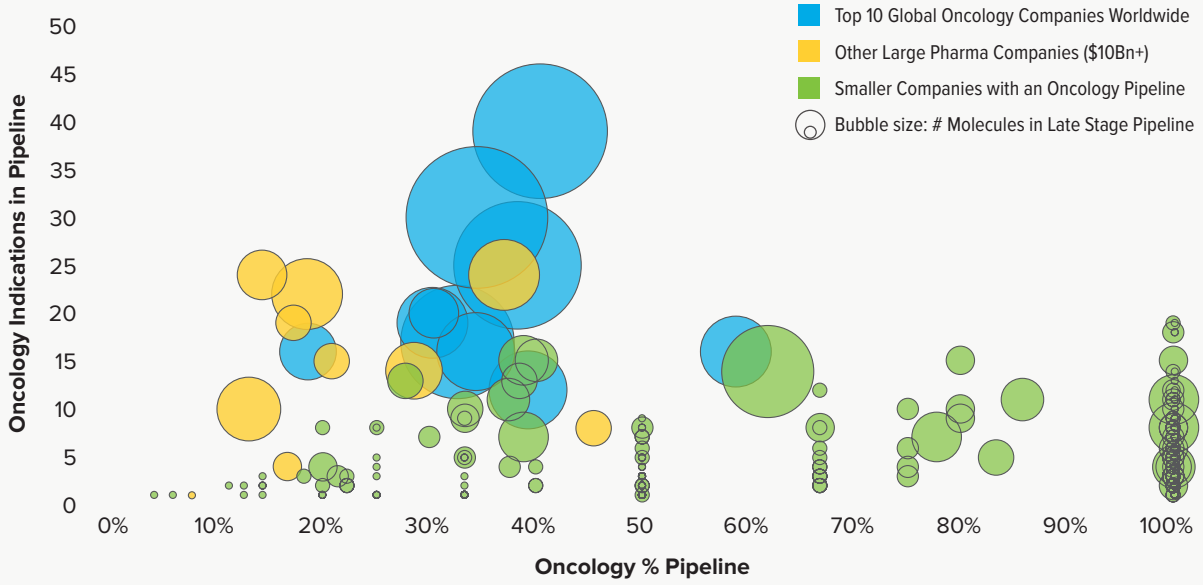
Antibody drug conjugates

Antibody drug conjugates (ADCs) and Antibody-dependent Cellular Cytotoxicity (ADCC) are two seemingly similar but quite different approaches to the targeting and delivery of cytotoxic agents to a tumor. ADCs attempt to bind to a cancer cell's antibody receptors and then transfer their cytotoxic payload in a targeted fashion with very little exposure of the cytotoxin to non-cancerous cells. Marketed drugs using this approach include breast cancer drug ado-trastuzumab emtansine (Kadcyla) which is an ADC of trastuzumab (Herceptin) with the cytotoxic agent emtansine. A range of ADCs are in development combining a variety of molecular and tumor targets. ADCCs coat a tumor cell with antigens that show affinity to the body's own death-inducing molecules killer such as macrophages, monocytes, neutrophils and others. In this way, ADCs deliver their own toxin to the tumor wrapped within the antibody, and ADCCs coat the target cells with an effective bullseye and wait for the body's natural killers to do the work. Each approach has obvious merit, but comparative research will bear out which are the more effective in patients.

Companies active in cancer

In addition and partly related to the panoply of drug mechanisms under development, the number and diversity of companies actively engaged in oncology R&D will remain significant. While history seems to favor large and experienced companies, familiar with the regulatory and logistical challenges of drug development and commercialization, a large and increasing group of smaller companies, some with only one drug in development, will continue to develop cancer medicines of all types. These smaller companies bring a narrow and specific expertise with a specific mechanism of action or a drug-development platform that offers a range of potential tumor targets, and their expertise is just as critical to the progress of cancer research as larger firms. Companies will likely pursue a range of strategies from go it alone, to partnerships, to the sale of their assets or often a combination of approaches. With all of this in mind, it is clear that a wide range of existing global companies and new participants will bring these cancer products to market over the next five years (see Exhibit 11).

Exhibit 11: Companies with Active Late Phase Oncology Pipelines



Source: Global Oncology Trend Report - A Review of 2015 and Outlook to 2020; Report by the IMS Institute for Healthcare Informatics, June 2016

Trends in U.S. medicines

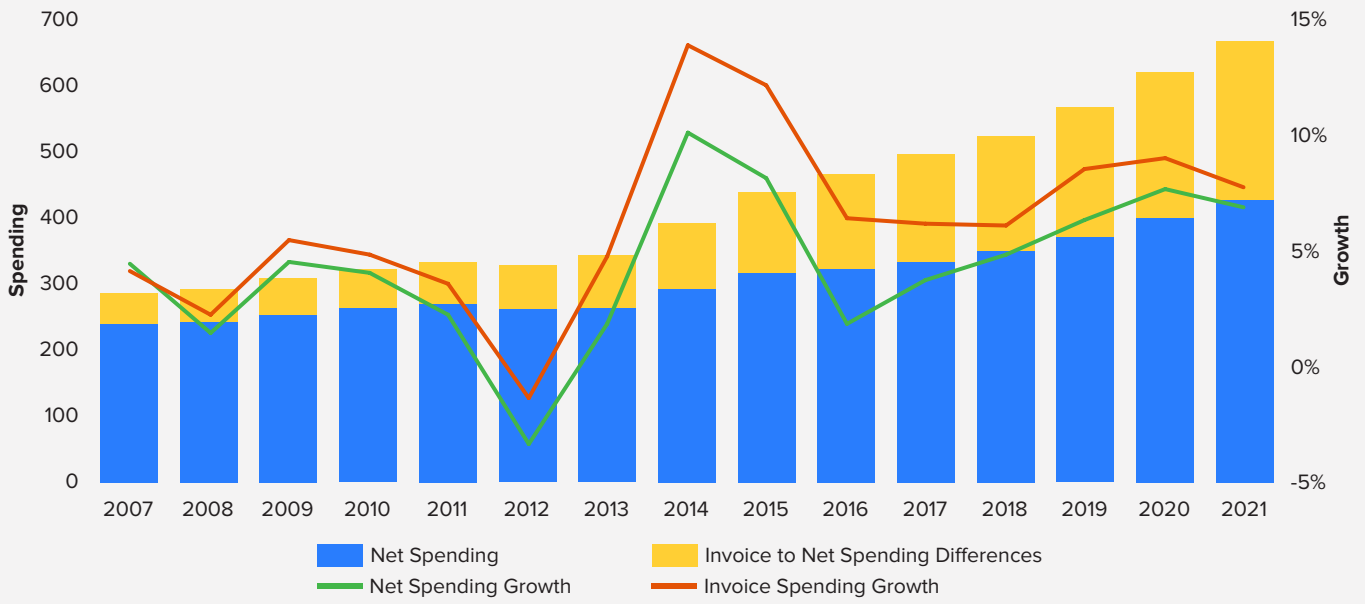
- U.S. market growth will slow by half in 2016 to 6–7% from 12% in 2015, and averages 6–9% through 2021
- Spending after estimated discounts and rebates will grow 4–7% to 2021
- Medicine costs will be driven by the transformative specialty brands, price increases and offset by rebates and lower cost generics
- Brand prices will increase more slowly at 8–11%, and net prices will increase at 2–5% from greater competition and price transparency
- Patient out-of-pocket costs will decline despite rising brand prescription costs as over 1/3rd of prescriptions will have $0 out-of-pocket costs as patients continue to receive copay assistance for brands, and shift to newly available generics
- The reduction in spending as branded medicines lose exclusivity is expected to total $143.5 billion in the next five years— over 1.5 times more impact than in the last five years —including the impact of biosimilars, which will account for between $27 and 58 billion
- Biosimilars are expected to have a significant impact on spending over the next five years with 25–35 in development, and a large percentage of them can be expected to reach the market in the U.S. by 2021 pending regulatory review and litigation

Spending and growth to 2021

Medicine spending growth in the U.S. had been slowing steadily since 2001, but rebounded sharply in 2014 and 2015 due to a lower level of patent expiry impact, historically high price increases for both brands and generics and the historic impact of breakthrough cures for Hepatitis C. Hepatitis C treatments alone accounted for 3% of the 12% growth in 2015, but are projected to decline slightly in 2016 and then grow modestly to 2021. In addition to these new breakthroughs, the last 2–3 years have seen a substantially higher level of spending on innovative drugs in other disease areas including cancer, autoimmune diseases, multiple sclerosis (MS) and diabetes. The removal hepatitis C as a significant growth driver in 2016, along with the increased level of patent expiry impact have combined to reduce the growth rate by half.

Over the past decade, the use of off-invoice discounts and rebates in contracts between manufacturers and intermediaries has become more widespread and pervasive with a widening gap between the so-called “gross” spending on medicines and the “net” realized revenue by manufacturers. These price concessions include statutory requirements for Medicaid and the Veteran’s Administration, as well as voluntary agreements with all types of insurers, as well as the value of patient copay assistance coupons and a number of other items. The QuintilesIMS Institute has estimated the scale of these concessions as the difference between QuintilesIMS audited medicine spending and manufacturer net realized revenues. The estimates include branded and generic medicines and ranged between 15–20% from 2007–11 rising to 28% in 2016 and projected to rise further to 36% by 2021 as list prices and levels of rebate concessions and patient copay assistance continue to increase.

Exhibit 12: U.S. Medicines Spending and Growth 2007–2021 US$Bn

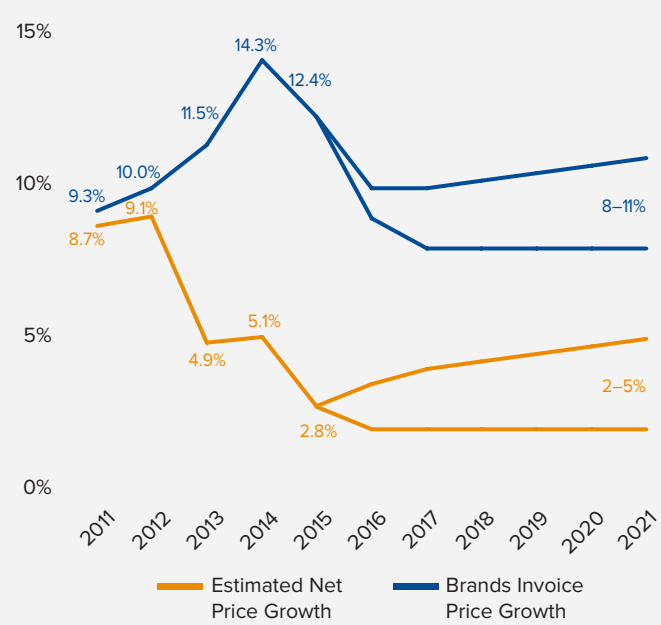


Source: IMS Market Prognosis, Sept 2016; QuintilesIMS Institute, Oct 2016

Over five years the U.S. will grow from $462 billion to $645–675 billion in 2021 on an invoice price basis, but from $318 billion to 405–435 billion in 2021 on a net basis (see Exhibit 12). One key element of the evolving invoice and net spending dynamics include the greater use of rebates and/or coupons for new medicines as payers exert their leverage in negotiations and attempt to control drug spending by limiting access to newer medicines. It is expected that manufacturers will continue to negotiate rebates and provide patient copay assistance similarly to the last few years with no major changes to the status quo, while it is also expected that rising patient exposure to costs makes these approaches even more necessary.

On an invoice basis, protected brands will average 8–11% invoice price increases over the next five years, returning to historic levels of price increases, and lower than historically high the 10–13% they averaged over the past 5 years. On a net basis prices will grow at 2–5% as markets are increasingly competitive and transparent (see Exhibit 13).

Exhibit 13: U.S. Protected Brand Invoice and Net Price Growth 2011-2021



Source: IMS National Sales Perspectives, QuintilesIMS Institute, Oct 2016

Pricing and patient out-of-pocket costs

While the incoming administration's policies around healthcare are still to take shape, it remains clear that medicine usage, pricing and reimbursement will remain influenced by the needs of key stakeholders. Pressures around pricing and calls for transparency which grew prior to the 2016 presidential election were driven primarily by historic increases in list prices of drugs. Unlike most traditional commercial insurance, list price increases directly affect patients in a Medicare part D plan with a standard donut-hole benefit design as well as those with high-deductible commercial or employer insurance plans, a type of insurance that has gained popularity in the past decade. As the sequence of congressional inquiries and media exposure mounted over 2015 and 2016, there has also been a notable slowing of list price increases for both branded and generic medicines during 2016. While these issues have generated a large amount of public frustration, we do not project any significant change in pricing mechanisms that inform Prescription Drug Plan (PDP) negotiated net prices in Medicare Part D. There are unlikely to be direct government price controls and it is highly likely that some form of the status quo mechanisms will continue through the forecast period.

The level of healthcare and medicine spending growth will remain more modest and policies in the new administration will contribute to that, though in different mechanisms and outcomes than the prior administration and the law under the ACA. New legislation will likely not take effect immediately and effects will grow in importance from 2018 and beyond, though they are expected to be only modestly different from the previous administration's scenarios.

Overall spending on medicines will increase based on the relative level of clinical improvement over existing options and the relative influence of stakeholders in driving greater use of lower cost options. Medicines which cure a disease or dramatically prolong life are not necessarily expensive, but increasingly that cost is coming under scrutiny. The price increases of existing branded and generic medicines are now routinely the subject of media coverage and political discourse. The issues of innovative drug pricing, existing branded price increases, discounts and rebates, and the pricing of generic drugs[15] are distinct issues, influenced by and impacting stakeholders differently, evolving at widely varying speeds and impacting patients and the overall system differently (see Exhibit 14).

While medicine spending is rising, patient out-of-pocket costs for prescription drugs at pharmacies are expected to decline slowly over the forecast period. This is driven by a range of factors including that patients are largely insulated from the rising cost of some specialty medicines when they reach an out-of-pocket maximum, or receive some form of copay assistance. Overall, out-of-pocket costs are declining due to greater generic availability, the expansion of Medicaid eligibility, and a related rise in the number of patients receiving prescriptions at zero out-of-pocket cost.

Generic drugs now account for nearly 90% of prescriptions, and that is projected to rise to 92% by 2021 as more medicines lose patent protection and rapidly shift to generics. Zero cost prescriptions accounted for 28.6% of prescriptions in 2016, 25% of all prescriptions were zero-cost generic drugs, resulting from plan designs which encourage lower cost drugs, or from Medicaid where 74% of prescriptions were dispensed with no cost, up 10 percentage points from 64% in 2011. Zero cost prescriptions will account for 34% of prescriptions by 2021, driven by mostly generic and older medicines.

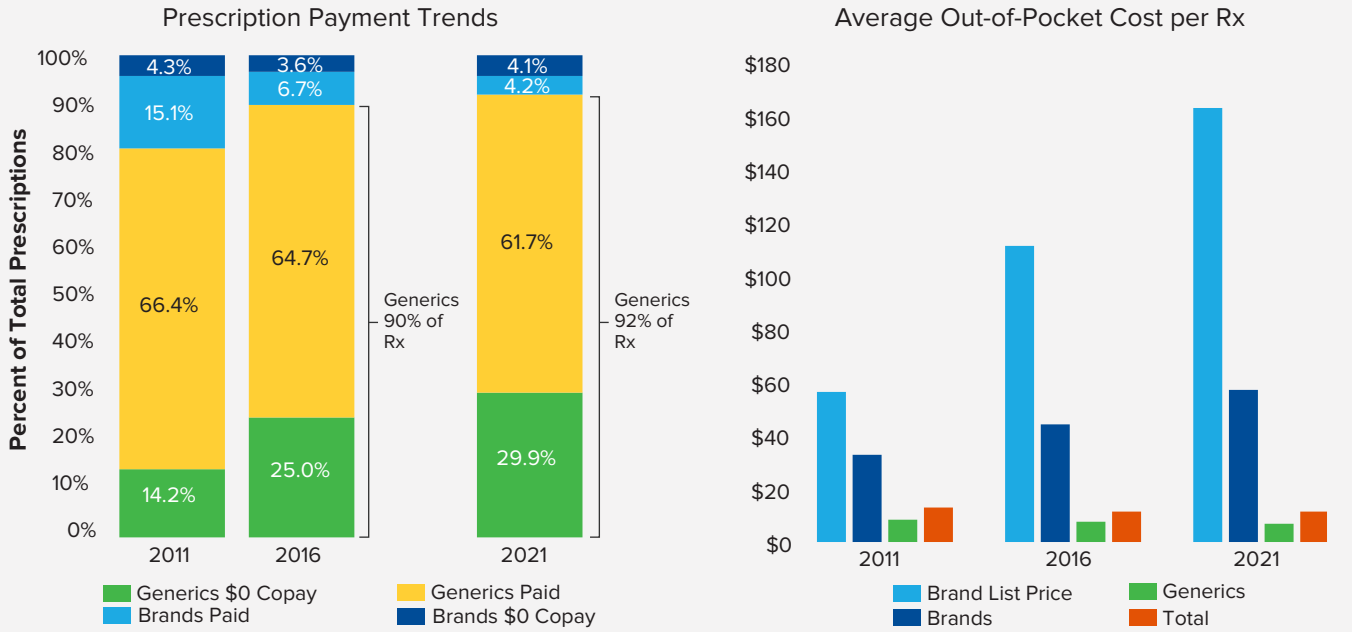
Exhibit 14: Outlook for U.S. Medicine Pricing through 2021

Component	Expectation	Comment
Price levels for new brands launched	Specialty brands are on average 15–20x more expensive than traditional new brands and more than half of new brand spending to 2021 will be specialty	Medicine spending grew by $148.2Bn over the prior five years Off-invoice discounts and rebates in the U.S. at nearly 30% compared to 17% in Europe and lower in the rest of the world
Price increases for protected brands (invoice)	8–11% brand increases expected to 2021	Reflects lower than the average 10–12% over past 5 years due to increased transparency, and competition
Pricing for protected brands on net basis	2–5% net price increases expected to 2021	Slightly higher than in 2015 net price growth of 2.8% which was affected by specific large competition-driven increases in rebates in Diabetes, Respiratory and HCV
Generic prices	Average generic is 60–70% below brand price upon introduction, reaching 80–90% after 2–3 years Older generic medicines pricing will have no impact on the growth forecast	Assumes continued generic pricing dynamics relative to pre-expiry branded price as observed over the past five years i.e. 60–70% below brand in first 6 months and 80–90% reduction after 24 months of generic availability Pricing of older generics is under scrutiny from payers and policy makers, the FDA is clearing a backlog of generic approvals and these pricing dynamics are unlikely to be a driver in the future

Source: QuintilesIMS Institute, Oct 2016

With greater numbers of patients enrolled in high deductible health plans through their employers or exchanges, overall costs will be relatively unchanged for patients paying an out-of-pocket cost for their prescriptions (see Exhibit 15). Generics are getting modestly cheaper as price competition drives down costs, while brands are getting more expensive on a list price basis, mitigated by coupons (for some patients) or insurance design. Where there is no generic or coupon available, and costs are high, patients will continue to abandon prescriptions. This projection assumes that the Medicaid expansion will not be reversed and that manufacturers will continue to fund patient savings programs to offset price increases and the rising use of high-deductible plans.

Exhibit 15: Outlook for Patient Out-of-Pocket Costs to 2021

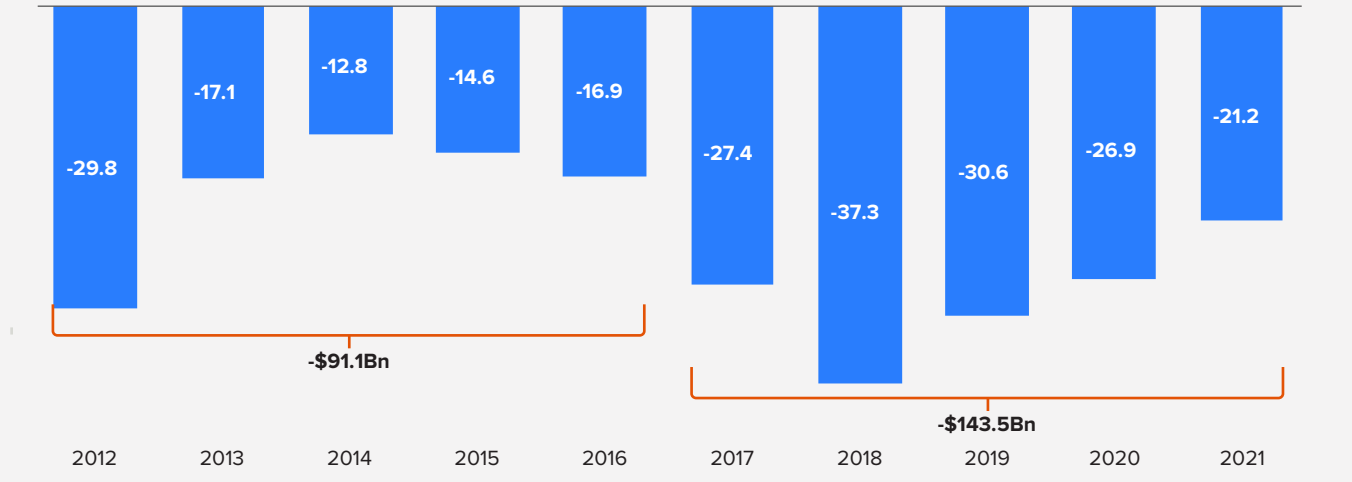


Source: IMS Formulary Impact Analyzer, Sep 2016; QuintilesIMS Institute; Nov 2016

Loss of exclusivity and biosimilars

Brand losses of exclusivity in the next five years are expected to have a 58%-greater impact on invoice spending compared to the last 5 years, which included the largest single-year impact to date in 2012 when $29.8 billion dollars of brand spending was lost primarily to lower cost generic options (see Exhibit 16). Lower brand spending due to patent expiries is expected to reduce overall spending by $143.5 billion in the next five years. The impact of losses of exclusivity includes the expected impact of biosimilars,[16] which were modeled under a variety of scenarios and represent 25–35% of the five-year impact in the base case included.

Exhibit 16: Impact of U.S. Losses of Exclusivity on Brand Spending US$Bn



Source: IMS Market Prognosis, Sept 2016; QuintilesIMS Institute, Oct 2016

A large number of biosimilar medicines are in development and can be expected to reach the market in the U.S. by 2021 (see Exhibit 17). There are significant uncertainties as many applications are not yet filed, regulatory reviews are not yet a frequent occurrence for FDA or the applicants, and almost all biosimilars will face litigation from originators.

Exhibit 17: Biosimilar Medicines Expected to be Available in the U.S. by 2021

Therapy Area	Molecule	Admin Route	# by 2021	Comments
Insulins	Insulin glargine	SC	1 approved currently (1–2 additional)	Approved, launch Dec 2016; Original insulins widely influenced by insurer non-medical incentives, biosimilars expected to follow similar patterns
Autoimmune	Infliximab	IV	1 approved currently (1–2 additional)	Approved, launch pending; Infused and reimbursed through medical benefit with significant provider incentives who are able to purchase for less than reimbursement level
	Adalimumab	SC	7–10	Self-administered but while expensive, most patients are insulated from cost through generous plan designs or coupons; Little switching due to cost between originators; In the absence of FDA approved interchangeability, patient financial incentives to choose biosimilars would be required to drive significant uptake. Patent litigation pending, biosimilars asserting 2018, originator 2022.
AMD	Ranibizumab	intra-ocular	1–2	Biosimilars for ranibizumab would require interchangeability and to discount similar to bevacizumab biosimilars. Interchangeability unlikely considering typical regulatory scrutiny of ophthalmic formulations.
Oncology Supportive Care	Filgrastim	IV	2 marketed currently (1–4 additional)	Non-original versions of Filgrastim including Granix and Zarxio have reached 40% of volume, growing slowly initially but accelerating with the addition Zarxio as the second competitor
	Pegfilgrastim	IV	2–3	The pegfilgrastim market is much larger than the filgrastim market and once a biosimilar or other non-original version is available similar uptake is expected
	Epoetin alfa	IV/SC	1–2	EPO usage in the U.S. is largely limited to chronic kidney disease with treatment paid for with bundled payments, making lower cost biosimilar an attractive financial option for providers
Oncology Therapeutics	Bevacizumab	IV	3–4	Widely used across multiple tumors, these cancer biologics will likely see similar uptake as that seen by Filgrastim to date. Off-label use of original bevacizumab in AMD likely to continue and biosimilar bevacizumab expected in 2019, a year before ranibizumab biosimilars.
	Trastuzumab	IV	2–3	
	Rituximab	IV	2–3	

Source: QuintilesIMS Institute, Sept 2016

The first biosimilar in the U.S. market, filgrastim (Zarxio) was approved in March and launched in September 2015, 21 months after another non-original version of filgrastim (Granix) launched in December 2013. Together the two have now captured 40% of the usage in the U.S., largely in line with volume penetration expectations. Savings were far below expectations as the price discounts versus the originator were not as great as many predicted, at least until the second competitor became available.

It is clear that the introduction of non-original competition for biologic medicines will contribute to a substantial level of savings for the U.S. healthcare system through 2021, however the rate and extent of the savings will depend on a number of factors unique to each medicine, therapy area, and the actions of the original and biosimilar manufacturers, as well as payers. The impact of biosimilars in the U.S. market could follow a range of scenarios ranging from short-term increases in cost to significant savings. Significant uncertainties could remain for several years with variations expected based on the characteristics of the product including administration and reimbursement as well as the presence of next-generation originators muting the value of the biosimilar medicine. In some cases greater use of a molecule which has limited biosimilar cost discounts could increase overall spending for a time, while in other cases deep discounts and wide usage could reduce spending by as much as 60% compared to the original biologic's spending. To best reflect these uncertainties, we modeled dozens of scenarios and summarized them into a range of outcomes (see Exhibit 18).

The key elements that are likely to govern market dynamics around biosimilars include:

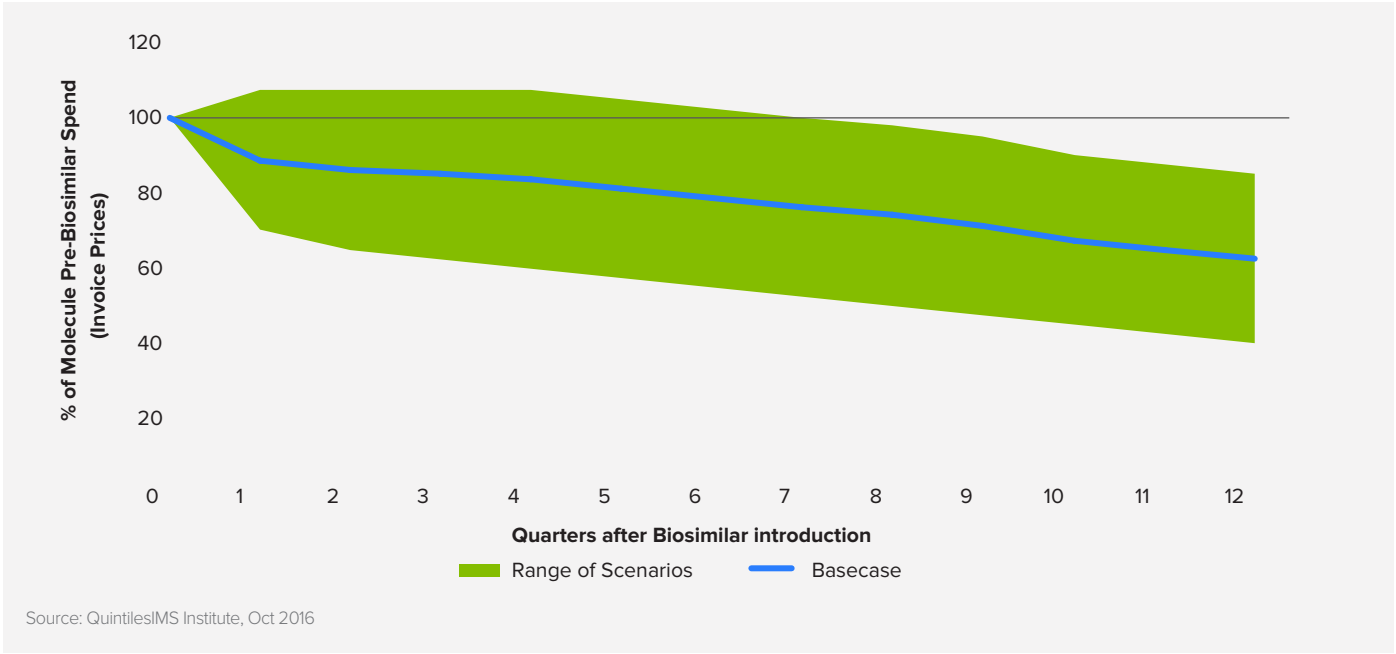
- **Reimbursement:** Medicines which are reimbursed through pharmacy benefits and under the control of a Pharmacy Benefit Manager may be incentivized differently than those reimbursed through the medical benefit with less direct insurer influence over a physician's prescribing decisions
- **Substitution:** Automatic substitution due to regulatory status and pharmacy rules or via incentives to providers or patients based on cost exposure
- **Competition:** Next generation originators in the same market reduce the relevance of the biosimilar and its reference molecule. The number of biosimilars will impact price discount levels offered by competing companies. Competitive responses from originators and the actions of insurers represent significant unknowns.
- **Litigation:** the timing of first and subsequent biosimilars could be delayed by complex litigation backed by limited legal precedents. These uncertainties will likely discourage early market entrants from reducing prices as rapidly as they would if expectations were more predictable or they were facing more competitors.

The extent to which PBMs have demonstrated influence over medicine choice is likely predictive of their influence under biosimilar scenarios, and as such, reimbursement will likely be tightly intertwined with substitution either via incentives or FDA-approved interchangeability, though there is still no clear guidance from the FDA how that would be granted.

An example of the confusing array of litigation is that which surrounds adalimumab, the biologic medicine with the highest spending in the U.S., which is likely to face 7–10 biosimilar challengers. The U.S. Patent and Trademark Office has declined to review a pair of AbbVie patents that Amgen contends are invalid, and with further challenges expected, it remains unclear whether the challengers will market their drugs in 2018 or will be prevented from doing so until AbbVie's patents expire in 2022.

Bevacizumab is expected to face biosimilar competition for its array of cancer indications by 2019, but it also raises an interesting potential scenario of whether there will be off-label use of biosimilar bevacizumab for age-related macular degeneration (AMD). While bevacizumab was never studied in AMD by its originator, Genentech, the National Eye Institute conducted a comparative trial of bevacizumab and ranibizumab (also developed by Genentech) and found both to be of similar efficacy and safety. Even prior to the NEI results, and because the two medicines use a very similar formulation and mechanism of action, doctors have used bevacizumab off-label in AMD. Due to dosing differences, the cost of bevacizumab when diluted to equivalent strength of ranibizumab is 1/40th the cost, and that cost difference was a key reason for off-label use and could have a large effect on the pricing of biosimilars of both molecules. If biosimilar bevacizumab becomes available, likely a year before biosimilar ranibizumab, a scenario could evolve where the FDA doesn't approve biosimilar bevacizumab for AMD, but doctors use it anyway.

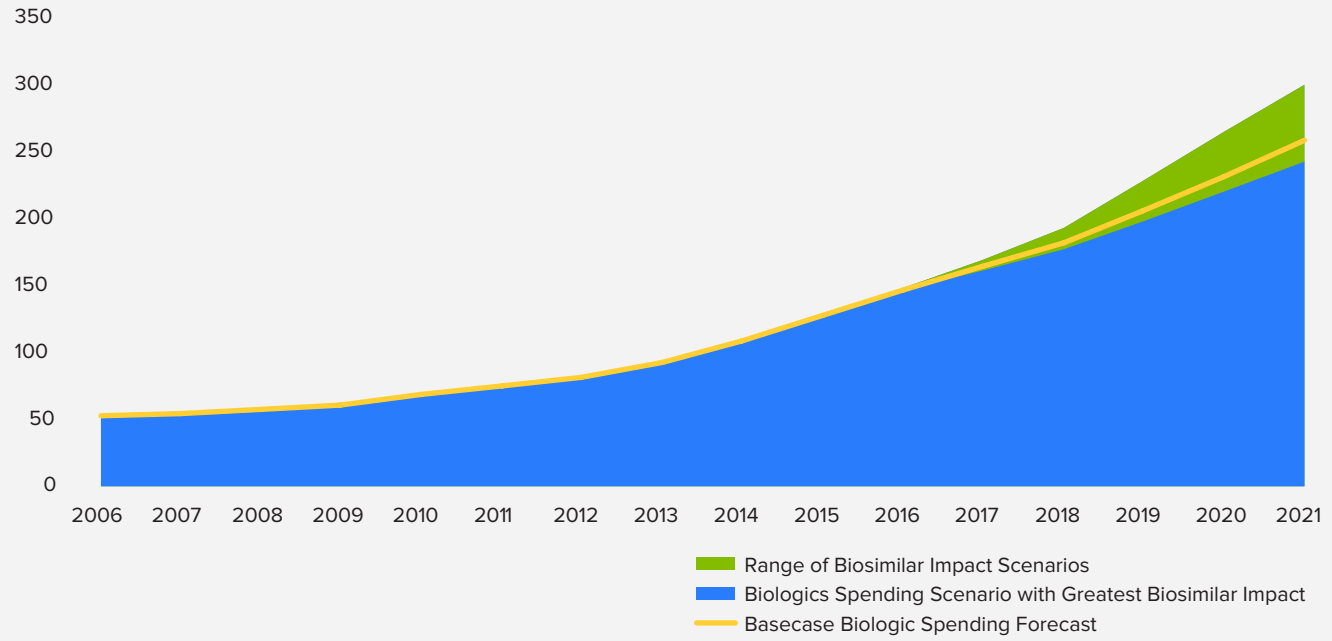
Exhibit 18: Biologic Molecule Spending Scenarios in the U.S. After Biosimilar Introduction



Source: QuintilesIMS Institute, Oct 2016

In the absence of biosimilars, biologic medicines would grow 14–17% per year through 2021 driven by new medicines for cholesterol, severe asthma, dermatological conditions, immuno-oncology and other immunology treatments. Biosimilar medicines will offset some of that growth, reducing spending by $27–58 billion, and lowering the biologics growth rate by as much as 5 percentage points to a 9–12% 5–year CAGR. The basecase forecast of 10–13% 5–year CAGR is based on the expected timing of biosimilar availability including the impact of regulatory reviews, litigation and the complex interactions of participating companies. (see Exhibit 19).

Exhibit 19: Total Biologic Market Spending in the U.S. – Scenarios to 2021 US$Bn



Source: QuintilesIMS Institute, Oct 2016

Pricing and growth in Europe

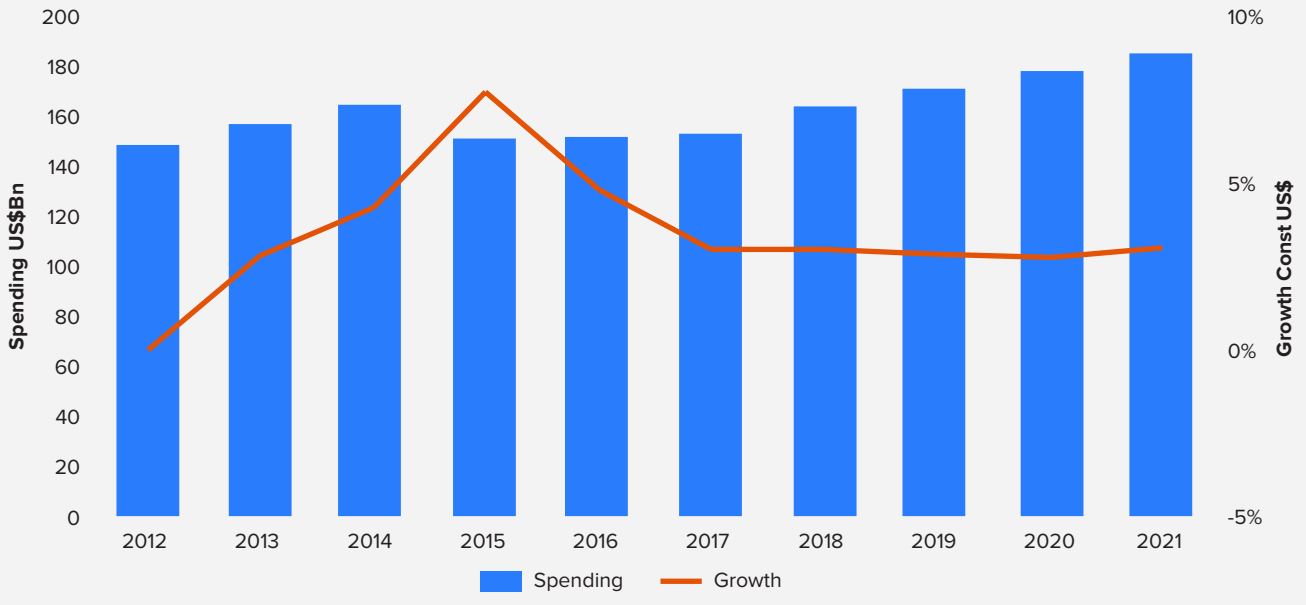
- Low pre-rebate and discount growth in the EU5 countries of 1–4% to 2021 is partly driven by policymakers responses to the surprisingly high new drug spending growth in 2014 and 2015, and they seek to control growth in the future
- The most pressing question for Europe outside pharma is around BREXIT, but the impact on the U.K. pharma market is expected to be modest at worst with a 1.5% slower growth rate in the downside scenario, yielding an average 4–7% growth to 2021
- The relatively weak economic growth in the region combined with the budget concerns arising from adopting (and paying for) recent innovations will encourage European payers to be more cautious in the adoption of newer medicines for some years to come
- Mechanisms to control price and/or access to innovative drugs continue to be the main tools used by European governments to manage spending on medicines and limit spending growth through the forecast period
- Fewer new launches in Europe are achieving price premiums, as few medicines are breakthroughs and the remainder are subject to more stringent levels of price limitation at launch

Spending and growth to 2021

Medicine spending in Europe will increase, at the pre-rebate/discount/list-price level from $151.8 billion in 2016 to $170–200 billion in 2021. Growth in the region will be 1–4% to 2021, as the U.K. grows (pre-rebate) at a rate of 4–7%, Italy and Spain grow at 1–4 %, France tightly controls growth at (–1)–2% and Germany grows at 2–5% (see Exhibit 20). Across the countries, 2015 saw the devaluation of the Euro and the British Pound to the U.S. dollar, reducing spending on a U.S. dollar basis by 8.3% from $164.7 billion in 2014 to $151.0 billion, but increasing by 7.7% on a constant US$ basis, which excludes exchange rate effects. The specific devaluation is not tied to nor specifically impacting pharmaceutical usage or spending, however macroeconomic challenges do influence government policies to some extent, especially considering the impact on the value of the British pound to the Euro and other currencies following the BREXIT referendum result.

Across the five major European markets, unexpectedly high medicine spending growth in 2014 and 2015—mostly driven by Hepatitis C treatment costs and coinciding with these economic issues—have prompted policy reactions that will seek to control growth in the future. In the U.K. and Germany, proposals have been made to limit sales of new medicines and trigger negotiations to avoid the unexpected budget-busters of the last two years. In France, policies will seek lower prices, greater generic usage and additional reforms to the payback system (where manufacturers repay the government if drug spend exceeds set levels). The reforms will also seek to carve out extra funding for innovative medicines to smooth annual fluctuations in expenditures. Italy will seek to control spending growth largely by shifting it to the hospital sector where government budgeting has greater direct control.

Exhibit 20: EU5 Countries Spending and Growth 2012–2021



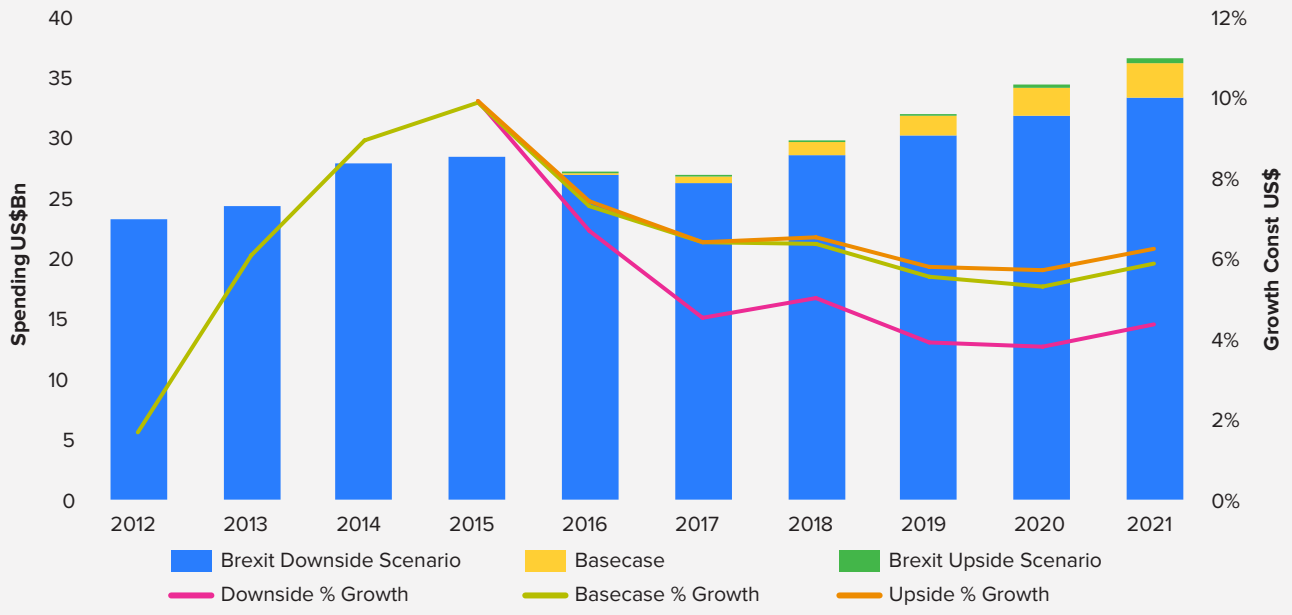
Source: IMS Market Prognosis, Sept 2016; QuintilesIMS Institute, Oct 2016

Spain's devolved regional budgeting approach is expected to continue to slow spending growth while leaving direct control over specific decisions to the regions. Germany is currently proposing changes to the market access and pricing system for drugs which will likely take effect in 2017 and may include continuing the price increase ban, which has been in force since 2009, until 2022, along with continuing evolution of its cost containment efforts around the AMNOG program of evaluating medicines' clinical value.

Impact of Brexit

The most immediate pressing question in Europe with direct effect on the pharmaceutical sector is the uncertainty around BREXIT, based on the unexpected referendum result in favor of the U.K. leaving the European Union. The most likely outcome is a minimal disruption to the industry and a negligible impact on medicine spending in the period to 2021 (see Exhibit 21). This is based on the timeframe necessary to negotiate and implement BREXIT, the continued importance of the U.K. as an industrial and commercial center, and the ongoing negotiations for BREXIT which are mitigating many of the worst potential outcomes that would impact medicine spending and the pharmaceutical industry. While the progress in negotiating BREXIT continues, Article 50 has yet to be invoked and the high court has indicated that the U.K. government must still gain parliamentary approval to do so—and the government has indicated it will appeal—leaving significant remaining uncertainties. There could be some modest increase in medicine spending above the basecase scenario if the U.K. government continues commitments to innovative drug access, especially with the number and quality of the innovations expected to 2021. The government has already indicated commitments, which while not directly related to medicine spending or the biopharmaceutical industry, would replace EU Horizon 2020 science and technology development funding with domestically sourced funds and likely retain and extend the accelerated access review program,[17] which speeds access to innovative drugs, and considerations to redirect Pharmaceutical Price Regulation Scheme (PPRS) drug rebates to help

Exhibit 21: Scenarios for Impact of Brexit on U.K. Spending and Growth 2012–2021



Source: IMS Market Prognosis, Sept 2016; QuintilesIMS Institute, Oct 2016

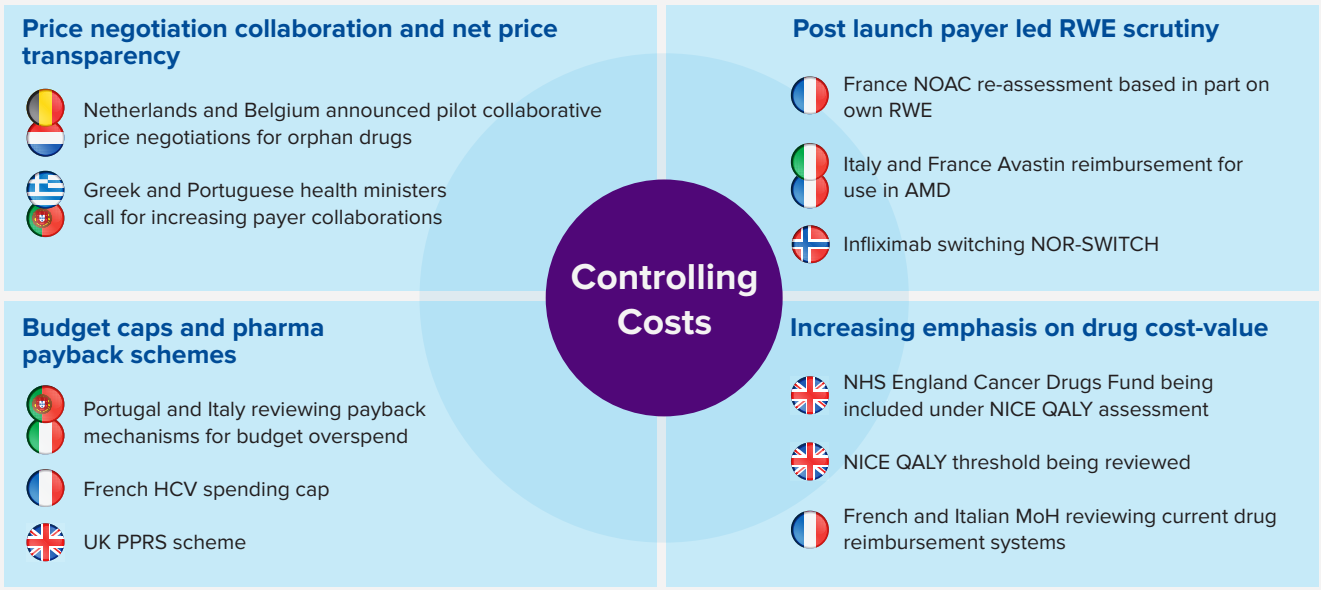
maintain funding for the Cancer Drugs Fund (CDF). Alternatively, there could be 1–1.5% slower growth in spending to 2021 based on more significant spending cuts. These downside scenarios include more focus on value for money reviews of new medicines by The National Institute for Health and Care Excellence (NICE), the impact of the reform of the dedicated Cancer Drugs Fund (CDF) now under the control of NICE and expected to be more restrictive, and potential for further cuts prompted by the NHS trusts' overspend in the last couple of years. Additional downsides could come from further devaluation of the British Pound, new trade barriers, or diverging regulatory pathways with the EU, events which could in any combination make the U.K. a less attractive market for innovators to launch medicines, and reduce spending on innovative medicines.

Controlling healthcare spending

Controlling healthcare and medicine spending is a uniform focus across European governments while policy approaches differ (see Exhibit 22). All of the countries in Europe seek to either control overall spending directly or indirectly by controlling price and access to specific drugs. Direct controls include spending or growth caps or payback schemes as in the U.K. or France. Other countries provide dedicated separate budgets for cancer or orphan drugs. Other indirect controls focus on evidence based assessment of the value of medicines which then influence either price, patient access to the medicines or both.

These approaches are largely collaborative with industry, and while none are entirely favorable to manufacturers, they are all generally intended to balance desirable medical progress with a nation's ability to pay on a sustainable basis. Price negotiation collaborations are better for both the countries and the manufacturers than arbitrary price controls and increasingly these approaches include confidential contractual tradeoffs based on price and volume. Examples of this pattern include the collaborative framework agreed to by Belgium, Netherlands, Luxembourg and Austria, which negotiates drug prices while agreeing to exchange data and coordinate evaluation methods across countries. In the past year the use of price and volume tradeoffs were signature elements of agreements for Hepatitis C treatment costs between manufacturers and governments such as Italy, Spain and France.

Exhibit 22: Recent Changes in Spending Control Mechanisms in Europe



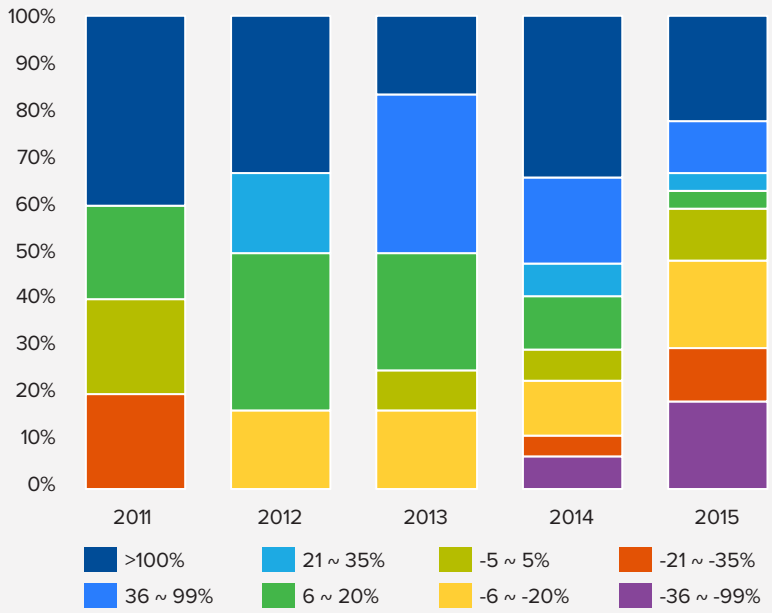
Source: QuintilesIMS Consulting Services, Jun 2016

The common themes across these developments are the focus on the overall aggregate "drug" budget rather than price alone, and a continuation of the policies that assess and/or control medicine pricing and access through clinical evaluations. The continued use of reference pricing schemes across markets raise challenges for manufacturers particularly as payers discuss greater transparency and cross-country cooperation around confidential discounts and rebates.

As a result of all of these policies, and despite an historic level of high quality innovation launched recently, fewer new medicines are achieving higher prices than existing comparator products in the market (see Exhibit 23). In general incremental innovations—those with only limited benefits over existing products—fare poorly in access and reimbursement negotiations. Health Technology Assessments (HTAs), which are now very common in Europe, are becoming more challenging both because of the overall budget pressure payers are facing, which is arguably raising the bar in these assessments, and because the products which are being reviewed are generally more incremental in nature. This is perhaps not surprising following a period of unusually transformative new products reaching the market, where the level of innovation or incrementalism is historically quite cyclical.

The presence and variety of cost, access and price control mechanisms belies the severity of the budget challenge governments face. On balance the 1–4% growth outlook for medicine spending over the next five years represents both an optimistic view for innovation and a continued commitment by payers to a sustainable biopharmaceutical industry, albeit an outlook less optimistic than the last five years.

Exhibit 23: Comparative Price Premiums of European New Medicines 2011–15



- 40% of 2015 NMEs analysed achieved a list price premium to the price comparator
- Oncology products account for the highest proportion of list price premiums in the overall 2015 NME cohort
- Only 35% of 2015 primary care NMEs analysed were priced at a premium vs. comparator

Source: IMS Pricing Insights
Notes: RX data only. Innovative Branded products only

Medicine use in pharmerging markets

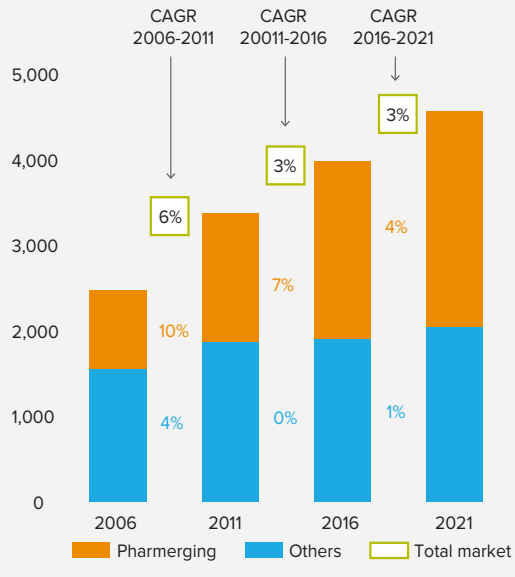
- Global expansion of the volume of medicines usage since 2011 is driven by pharmerging markets but is slowing
- Slowing macroeconomic growth in pharmerging markets is impacting medicine usage
- Per capita medicine spending has wide variations with some countries far lower than others
- Derailed commitments and delayed, revamped or cancelled expansion programs have been caused by a weaker economic environment
- Volume growth continues to be driven by non-original products
- The outlook for spending growth is slowing across the pharmerging markets

Spending and volume growth to 2021

The volume of the use of medicines is projected to increase by a 3% compound annual growth rate globally in the next five years compared to 6% from 2006–11 and 3% from 2011–16 (see Exhibit 24). The global volume will have increased from nearly 2.5 trillion doses of medicines (standard units) in 2006 to almost 4 trillion doses in 2016 with ¾ of that growth from pharmerging markets. The rest of the world in aggregate, including developed countries and 190 other countries around the world, will see essentially unchanged per capita rates of medicine usage over the next five years. Pharmerging markets will continue to expand access and usage of medicines at a rate of approximately 4% per year compared to a projected population growth rate of 0.8%.[18]

People in pharmerging countries will consume more than half of the medicines used globally, consistent with the more than half of the world's population who live there.

Exhibit 24: Global Medicine Volume Growth 2006–2021, Standard Units Bn



Source: QuintilesIMS Institute, Oct 2016

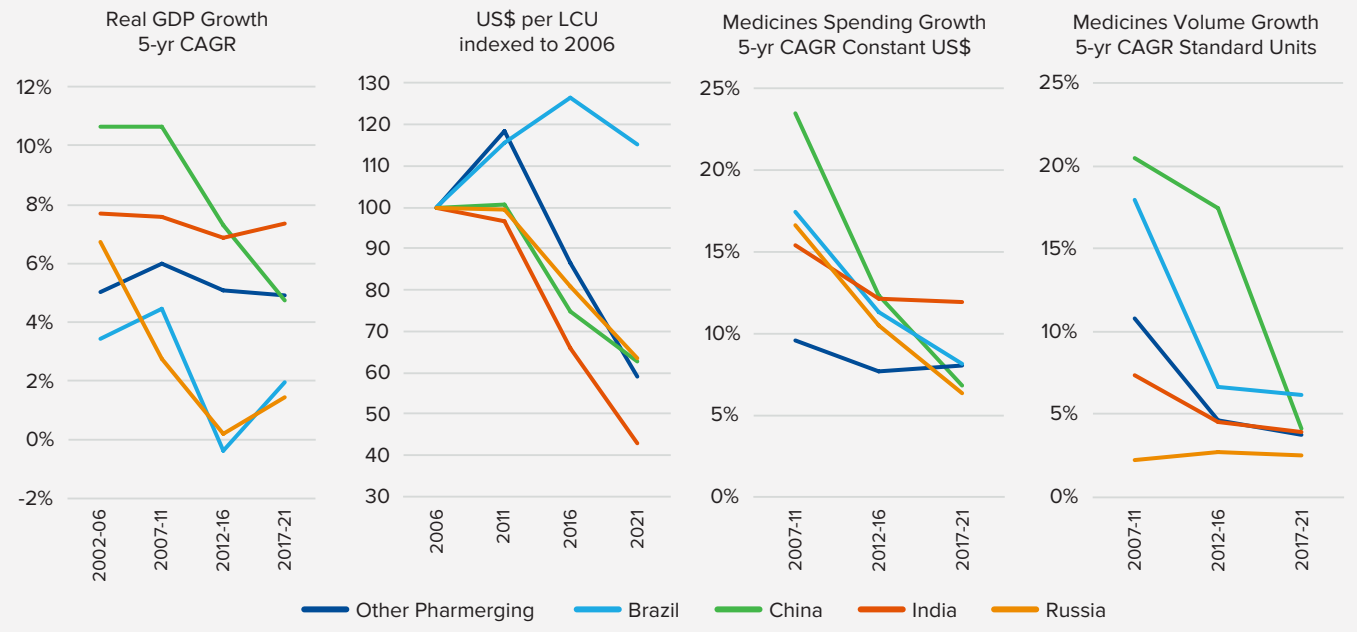
The evolution of pharmerging markets away from being "left-behind" is being interrupted by the current economic climate, but progress will continue to be made. That 90+% of medicines used in pharmerging markets are non-original products is a key element that both enables their progress in advancing health and ultimately limits how attractive the countries will be for pharmaceutical investments, and therefore whether access is gained to the newest medicines as quickly as in the more developed markets.

Pharmerging markets volume of medicine usage grew by an average 10.3% from 2007–11, slowing to 6.6% from 2012–16, and projected to slow further to 3–6% from 2017–21.

Improvement in the economies of pharmerging markets have been the key driver of greater medicine use, contributing both to governments' policies to expand healthcare provision as well as to personal incomes which drive so much of the medicine purchases in pharmerging markets.

As economic prosperity accelerated, volume growth followed, but as growth has now slowed and currency exchange rates to the dollar have weakened, medicine spending and volume growth have slowed as well (see Exhibit 25).

Exhibit 25: Pharmerging Market GDP Growth, Exchange Rates, Medicine Spending and Volume Growth

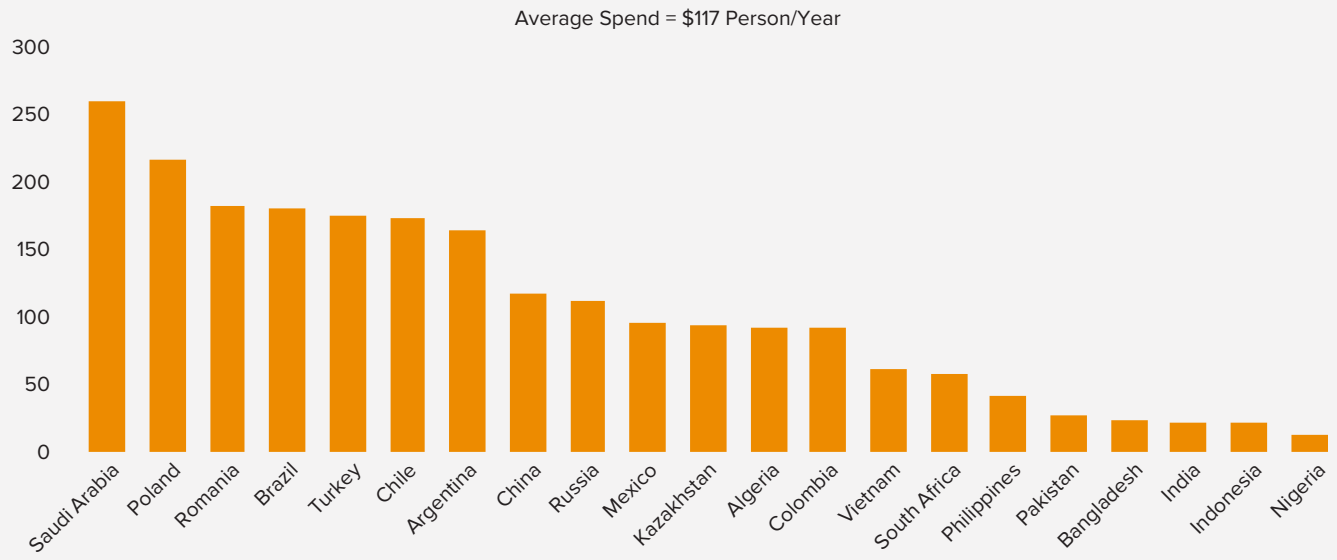


Source: Economist Intelligence Unit; IMS Market Prognosis, QuintilesIMS Institute, Sept 2016
Chart notes: Chart shows 5-year CAGR except for currency exchange rates where specific years are shown indexed to 2006

Medicine spending per capita in pharmerging markets remains very low compared to developed markets, with pharmerging markets averaging $117 per person per year in 2021 compared to $1,955 in the U.S., $776 in Canada, $739 in Japan, $577 in the five major European markets, $513 in Australia and $295 in South Korea.

Asian markets including India, Pakistan and Bangladesh all spend from $20–30 per person per year (see Exhibit 26). Medicines can often be provided to patients relatively cheaply, without a country making the full investment of a robust healthcare infrastructure, and these relatively low per capita spending values are suggestive of significant remaining healthcare gaps where millions lack access to basic healthcare services.

Exhibit 26: Pharmerging Countries Medicines Spend per Capita in 2021 Constant US$



Source: IMS Market Prognosis, Sept 2016; QuintilesIMS Institute, Oct 2016
Note: Spending per capita, per capita growth and overall spending growth in Constant US$

Derailed commitments and expansion programs

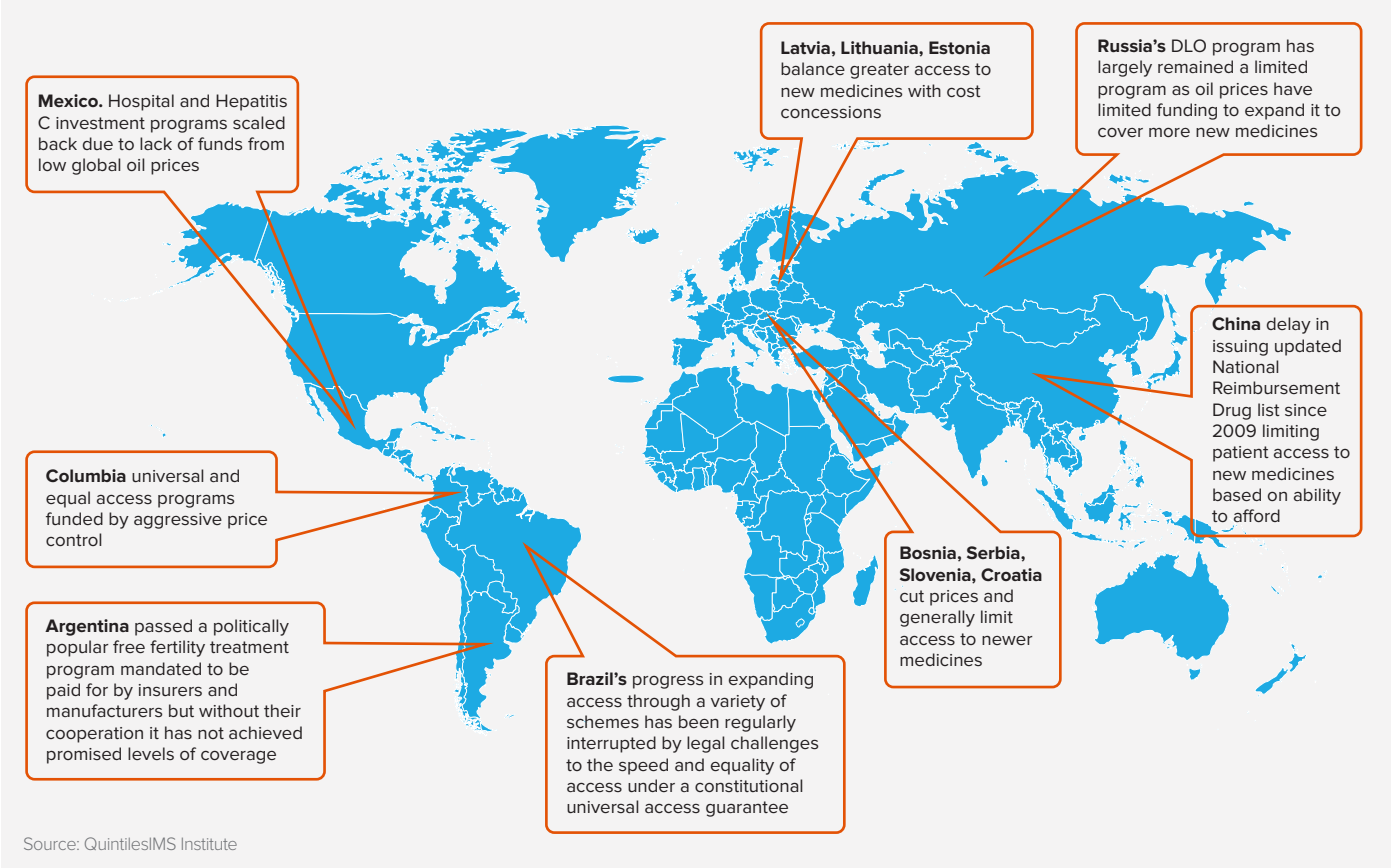
With much of the growth in volume and spending driven by macroeconomic growth in the past decade—driven by investment which flooded into pharmerging markets—many countries committed to policies that would expand access to more of their people, with the expectation that the growth and increased investment would continue. As the global economy has slowed, countries are balancing their new economic realities with the commitments they had previously made. In the last two years, a number of policies have either been adjusted, delayed or cancelled as the conditions and necessary funding for them has dried up (see Exhibit 27). Some leaders have found it challenging to overtly back out of promises to their people and they have instead shifted focus to renegotiating terms with pharmaceutical manufacturers.

Most of these countries are in the midst of longer term efforts around “gap management” or “system upgrades” linked to societal expectations. While each country is different, the level of expectation for basic levels of healthcare rises with economic growth and incomes. One area of investment has been in cancer funding, where countries in Central and Eastern Europe have committed funding for detection and treatment of preventable cancers such as breast, cervical and colon cancer with positive results in reduced mortality.[19]

Efforts to leapfrog technologically, adopting electronic health systems as part of system reforms, was hailed as the way pharmerging markets would rapidly catch up to developed markets, but there has been only slow progress in many markets.

For countries with limited budgets, some have been negotiating with the pharmaceutical industry for across the board price cuts, additional discounts in return for market access, and caps on medicine spending linked to specific expected levels of spending. Some are even demanding free medicines for a period prior to listing for reimbursement. These patterns highlight the aspirations to close healthcare gaps with developed markets and use the best and latest treatments, but present sustainability and commercial attractiveness challenges to the industry.

Exhibit 27: Promised Patient Healthcare/Medicine Access Expansions Adjusted, Delayed or Canceled Due to Economic Conditions



Source: QuintilesIMS Institute

In China, the National Reimbursement Drug List (NRDL) which provides reimbursed access to medicines, was hailed as a cornerstone of China's historic access expansion and quality improvement program when it was introduced in 2000, and updated in 2004 and 2009. However, hundreds of new medicines have been approved since the last update and are not widely available in China. Similarly, Russia announced the DLO program in 2007 to separately fund and manage high cost specialty medicines, but economic troubles, largely due to low global oil prices, have limited the funding for the program.

In some situations, simplistic approaches to cost containment actually harm domestic producers, as in Bosnia and Herzegovina where the reference pricing policy pegged prices to regional neighbors (Serbia, Croatia, Slovenia) but cut prices for domestic companies, some of which are government owned. Colombia's universal and equal access programs are funded by aggressive price controls, but in turn make the country less attractive to international companies and limit access to newer medicines.

The recent availability of cures for Hepatitis C have prompted countries around the world to dedicate funding to treat their populations, often then finding it challenging as unexpectedly large numbers of patients seek treatment. Other countries, like Egypt, with the world's highest rate of Hepatitis C infection, have been able to negotiate preferential pricing in return for policies to prevent a gray market in otherwise expensive treatments. Keeping the promise to cure curable diseases has significant costs and political leaders are balancing relatively weak economies, low commodity prices and popular expectations in a delicate balance.

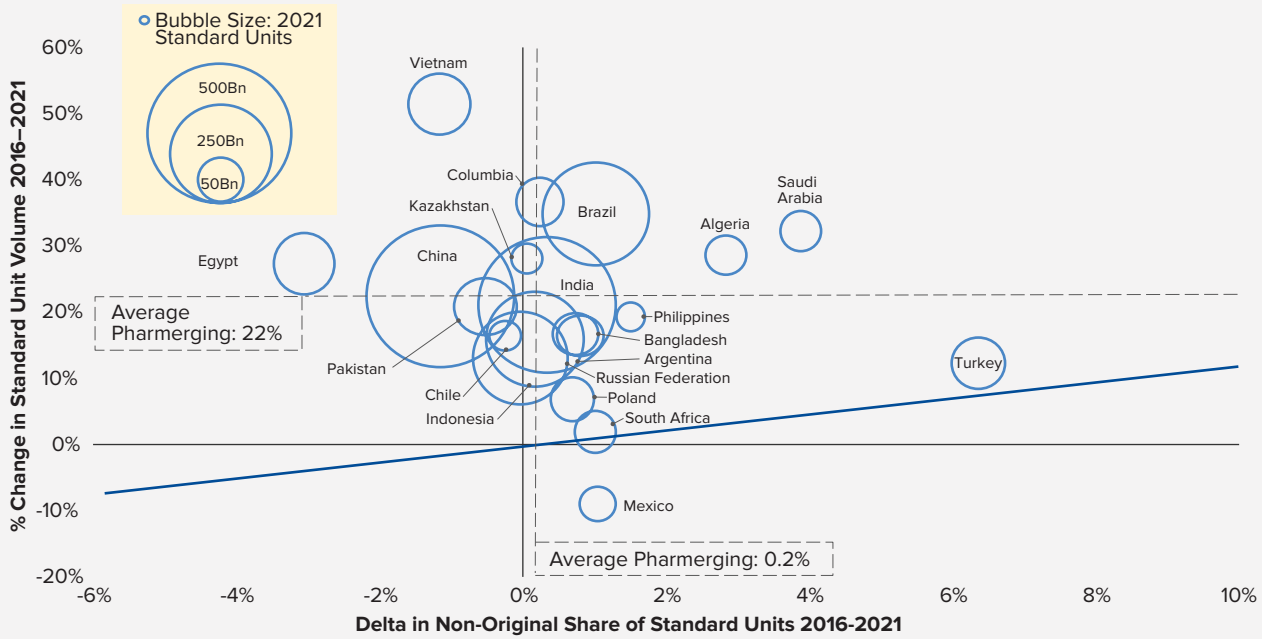
For countries heavily dependent for revenues on oil, low global prices have a direct effect on health, as in Mexico where the hospital investment program has been scaled back due to national budget deficits driven by weak oil exports.

Brazil finds itself in a relatively unique trap because of a constitutional provision guaranteeing universal and equal access to healthcare. Government efforts at cost containment have been repeatedly challenged by the judiciary with rulings that obligate the government to provide high cost treatments that exceed available budget funding. Programs for low income citizens have been very popular but costs have ballooned and overall budget pressure has forced cuts and will eventually force more.

In some cases, access to medicines is so politically popular, policies are implemented with no path to funding them, as with Argentina's free fertility treatment law, which was wildly popular during an election, but funded entirely through a mandate to the private insurance industry. Weak controls and insurer resistance has resulted in a significant gap between the promised and actual coverage, frustrating patients. In general, access to medicines represents a wildly popular political issue but funding it remains challenging for countries up and down the income ladder.

In most cases, these access programs are focused on decades-old or generic medicines and for the most part pharmerging markets are driven by non-original products, averaging 91% of volume across the group of countries. Non-original medicines include unbranded generics, branded non-original products or "branded generics" copy products, over-the-counter (OTC), and traditional medicines, which are widely used in some countries. Over the next five years the average volume share of non-original products is projected to rise 0.2% on average, while overall volume is expected to increase by 22% (see Exhibit 28).

Exhibit 28: Phamerging Volume Growth and Change in Non-Original Volume Share



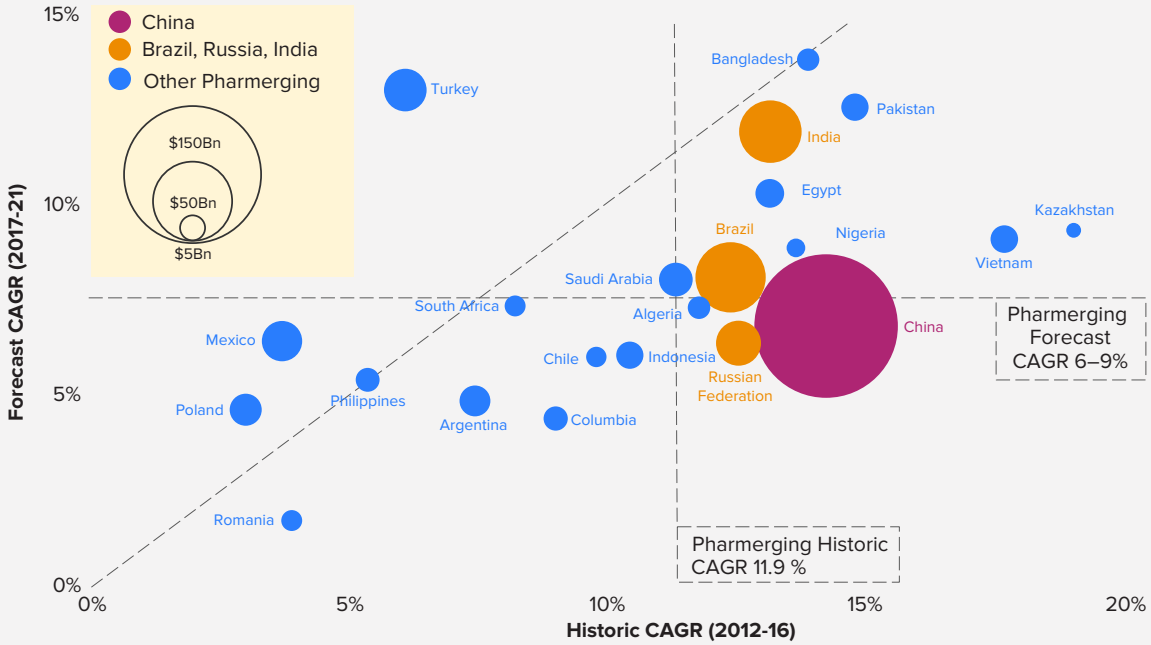
Source: IMS Market Prognosis, QuintilesIMS Institute, Oct 2016

Medicine spending, when both volume dynamics—growing on average 4% to 2021—and the adoption and costs of originator branded products are included, will grow an average of 6–9% to 2021.

The only countries expected to accelerate spending growth over the next five years are Turkey with a significant double-digit growth expected, and Mexico and Poland with more modest growth. Turkey's medicine spending growth outlook will be driven by continued double-digit growth in healthcare overall and particularly hospital infrastructure expansion, but generally offset by compulsory discounts to the social security budget (SGK), likely growing in low single digits after these discounts are applied. The outlook in Mexico and Poland reflects a continuation of the trend in the last five years when they had the slowest growth across pharmerging markets. Romania, Argentina, Colombia and Poland are all expected to grow by less than 5% to 2021.

China is the largest pharmerging market, reaching $150–180 billion by 2021, but it will face slowing growth from 14.3% in the last five years to less than 7% in the next five years. With over 95% of the population now covered by insurance, incremental medicine volumes will slow, and government priorities are now shifting to harmonizing the coverage insurance provides, which in turn is raising questions of pricing and access to medicines. A key challenge is managing hospital spending, which accounts for 63% of China's medicine spending, with reforms focused on restructured financing in a bid to remove the profit motive from hospital drug purchases. The policies have already had significant effects on drug spending growth in 2015 and 2016 and, along with slower expected volume growth, are the key contributors to the slower expected 5–8% growth to 2021, down from 12.5% CAGR from 2011–2016 (see Exhibit 29).

Exhibit 29: Pharmerging Markets Historic and Forecast Spending Growth



Source: IMS Market Prognosis, Oct 2016

Notes on sources

IMS Market Prognosis™ is a comprehensive, strategic market forecasting publication that provides insight to decision makers about the economic and political issues that can affect spending on healthcare globally. It uses econometric modeling from the Economist Intelligence Unit to deliver in-depth analysis at a global, regional and country level about therapy class dynamics, distribution channel changes and brand vs. generic product spending.

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

IMS Disease Insights provides in-depth country level analysis of nine diseases: Alzheimer's, Asthma, Diabetes, COPD, Parkinson's, Melanoma, Stroke Prevention in Atrial Fibrillation, Prostate Cancer and Rheumatoid Arthritis. The offering produces a total of 81 country-specific disease analyses. Disease Insights includes an overview of each disease and available treatment options along with a detailed view of the market and a forecast for approximately 640,000 facilities.

IMS LifeCycle™ **New Product Focus**™ is a comprehensive worldwide tracking service of historical product launches since 1982. It includes information about product launches in each country, including the indication and price at the time of the initial launch, and covers more than 300,000 launches.

IMS LifeCycle™ **R&D Focus**™ is a global database for evaluating the market for medicines, covering more than 31,000 drugs in R&D and over 8,900 drugs in active development worldwide. It includes information about the commercial, scientific and clinical features of the products, analyst predictions of future performance, and reference information on their regulatory stage globally.

IMS PharmaQuery™ is an online research tool designed to unravel the complexities of pricing and reimbursement in 31 key world markets. It provides detailed information on the rules and regulations, theories and practices, trends and developments, in pricing and reimbursement in both developed and emerging markets.

IMS Therapy Prognosis™ Includes sales forecasts for major therapy areas in 14 key markets, 8 developed (U.S., Japan, Germany, France, Italy, Spain, U.K., Canada and South Korea) and 6 pharmerging (China, Brazil, Russia, India, Turkey and Mexico) and includes interactive modeling and event-based forecasts and comprehensive market summary.

IMS Formulary Impact Analyzer (FIA) provides insight into what impact popular utilization-control measures enforced by managed care organizations have had on prescription volumes including the dynamics that affect patient behavior in filling and/or refilling prescriptions. FIA provides analysis of the out-of-pocket cost paid by patients with all kinds of insurance coverage. Formulary measures include tiered copay benefit designs, prior authorization restrictions. FIA sources include national and regional chains, independent pharmacies and a switch house providing a comprehensive view of retailers and across geographies.

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About the QuintilesIMS Institute

The QuintilesIMS Institute leverages collaborative relationships in the public and private sectors to strengthen the vital role of information in advancing healthcare globally. Its mission is to provide key policy setters and decision-makers in the global health sector with unique and transformational insights into healthcare dynamics derived from granular analysis of information.

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 patient care. With access to QuintilesIMS's extensive global data assets and analytics, the Institute works in tandem with a broad set of healthcare stakeholders, including government agencies, academic institutions, the life sciences industry and payers, to drive a research agenda dedicated to addressing today's healthcare challenges.

By collaborating on research of common interest, it builds on a long-standing and extensive tradition of using QuintilesIMS information and expertise to support the advancement of evidence-based healthcare around the world.

Research Agenda

The research agenda for the Institute centers on five areas considered vital to the advancement of healthcare globally:

The effective use of information by healthcare stakeholders globally to improve health outcomes, reduce costs and increase access to available treatments.

Optimizing the performance of medical care through better understanding of disease causes, treatment consequences and measures to improve quality and cost of healthcare delivered to patients.

Understanding the future global role for biopharmaceuticals, the dynamics that shape the market and implications for manufacturers, public and private payers, providers, patients, pharmacists and distributors.

Researching the role of innovation in health system products, processes and delivery systems, and the business and policy systems that drive innovation.

Informing and advancing the healthcare agendas in developing nations through information and analysis.

Guiding Principles

The Institute operates from a set of Guiding Principles:

The advancement of healthcare globally is a vital, continuous process.

Timely, high-quality and relevant information is critical to sound healthcare decision-making.

Insights gained from information and analysis should be made widely available to healthcare stakeholders.

Effective use of information is often complex, requiring unique knowledge and expertise.

The ongoing innovation and reform in all aspects of healthcare require a dynamic approach to understanding the entire healthcare system.

Personal health information is confidential and patient privacy must be protected.

The private sector has a valuable role to play in collaborating with the public sector related to the use of healthcare data.

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