The Future of the Global Pharmaceutical Industry

October 2017
## Table of Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Executive Summary</td>
<td>3</td>
</tr>
<tr>
<td>2. Pharmaceutical Sector Has Grown Rapidly in the Last Century</td>
<td>7</td>
</tr>
<tr>
<td>- Widespread concerns about the sector today</td>
<td>8</td>
</tr>
<tr>
<td>- Thousandfold increase in value of companies in sector since 1920s</td>
<td>10</td>
</tr>
<tr>
<td>3. Pharmaceutical Sector Will Triple in Size in the Next 40 Years</td>
<td>12</td>
</tr>
<tr>
<td>- Pharmaceutical consumption econometrically close related to GDP growth</td>
<td>14</td>
</tr>
<tr>
<td>- Based upon expected GDP growth, the pharma sector will likely triple in size by 2060</td>
<td>19</td>
</tr>
<tr>
<td>4. Total Value of the Pharmaceutical Sector Today over $5 Trillion</td>
<td>20</td>
</tr>
<tr>
<td>- Total revenue in the pharma sector around $1.1 trillion in 2017</td>
<td>23</td>
</tr>
<tr>
<td>- Total value of companies in sector over $5 trillion. Pharma one of the world’s largest sectors</td>
<td>24</td>
</tr>
<tr>
<td>5. Pharma Will Be Positively Impacted by Growth in Rare Disease Drugs and China</td>
<td>27</td>
</tr>
<tr>
<td>- Cost controls widespread and likely to continue. Major impact on Europe market</td>
<td>28</td>
</tr>
<tr>
<td>- Rare disease pharma sector has grown in value by 1300% since 2000. To continue growing fast</td>
<td>37</td>
</tr>
<tr>
<td>- China to become a close #2 to the U.S. market in time. Dramatic growth to continue</td>
<td>49</td>
</tr>
<tr>
<td>6. Innovations in Inflammation Control, Nucleic Acids and Implantables Will Transform Industry</td>
<td>55</td>
</tr>
<tr>
<td>- Better Manufacture Will Facilitate Dramatic Growth in Peptide Therapeutics</td>
<td>56</td>
</tr>
<tr>
<td>- Control of Inflammation May Substantially Reduce Mortality from Cancer &amp; Heart Disease</td>
<td>61</td>
</tr>
<tr>
<td>- Nucleic Acid Therapeutics a Source of Substantial Future Growth</td>
<td>65</td>
</tr>
<tr>
<td>- Cell Therapy is Becoming Mainstream in the Pharmaceutical Industry</td>
<td>70</td>
</tr>
<tr>
<td>- Implantables and Electroceuticals Will Redefine Therapeutic Sector</td>
<td>74</td>
</tr>
<tr>
<td>7. Summary</td>
<td>84</td>
</tr>
<tr>
<td>A1. About Torreya</td>
<td>93</td>
</tr>
</tbody>
</table>
1. Overview

Executive Summary
We at Torreya are engaged in providing strategic advice to companies in the life sciences industry and have compiled a comprehensive global database of companies in the pharmaceutical sector. We have analyzed key trends in pharmaceuticals and have built a model relating pharmaceutical revenue over time and place to fundamental economic factors. We have used this model to forecast pharma revenues at the country level out to 2060.

This report focuses on the most important trends and innovations that will shape the pharmaceutical sector and impact human life in the decades ahead.

The analysis and observations in this report were compiled by Torreya in the Fall of 2017. We have focused on ideas and trends that we observed in both the scientific literature but also in discussions with client companies in recent years. Our analysis is by necessity incomplete and does not comment in detail on a number of important trends associated with aging, the rise of cell therapy, pricing pressure on generics, consolidation in drug wholesaling, digital health, the growth of biologics etc.

We are grateful to many individuals who helped us with the insights in this report and the underlying database used herein including: Elizabeth Condo, Torreya; Pam Demain, formerly of Merck; Chuck Dimmler, Torreya; Masaki Doi, Torreya; Benjamin Garrett, Torreya; Weijun Gu, JPT; Kylor Hua, Torreya; Jeremy Ji, JPT, Stephanie Leouzon, Torreya; David Paterson, Impax Laboratories, Melissa Pearlman, Torreya, Alan Selby, Torreya and Ping Shek, Torreya.

All opinions and forecasts are our own and may prove to be inaccurate. All errors and omissions are our own and the information in this report, particularly that on private companies, may be inaccurate, dated or, at best, directional. All content in this report is subject to the disclaimer provided on page 92.
Where has the pharma industry been?
Where is the pharma industry going?
What is the composition and size of the sector today?
What trends and innovations that will shape the industry in the future?
Executive Summary

- Growth in the pharmaceutical industry will be driven by increasing wealth across the world.
- The pharmaceutical industry is likely to triple in size by 2060 on an inflation-adjusted basis.
- The pharmaceutical industry is around 30% larger than previously thought and is one of top five in the global economy.
- Major innovations will continue to drive the size and growth of the industry with positive implications for the health of the global population.
2. Where Have We Been?

Pharmaceutical Sector Has Grown Rapidly in the Last Century
Major Concerns About the Pharma Industry and the Medical Sector

Nov 2014: “There are already signs of trouble ahead - thousands of job losses and widespread consolidation are hardly characteristics of an industry in rude health...

‘Little breakthrough’
For a start, big pharmaceutical companies are no longer providing the service they once did.

"The system has served us well in terms of developing good new medicines, but in the past 10-20 years there has been very little breakthrough in innovation," says Dr Kees de Joncheere at the World Health Organisation.

Of the 20 or 30 new drugs brought to the market each year, "many scientists say typically three are genuinely new, with the rest offering only marginal benefits," he says.”

"Tomorrow’s challenge is to develop new medicines that can prevent or cure currently incurable diseases. Today’s challenge is to get to tomorrow – and that’s a tall order in itself.

Rising customer expectations: The commercial environment is getting harsher, as healthcare payers impose new cost constraints on healthcare providers and scrutinize the value medicines offer much more carefully.

Poor scientific productivity: Pharma’s output has remained at a stable level for the past decade. Using the same discovering and developing processes, there’s little reason to think its productivity will suddenly soar.

Cultural sclerosis: The prevailing management culture, mental models and strategies on which the industry relies are the same ones it’s traditionally relied on, even though they’ve been eclipsed by new ways of doing business.”

The combined market cap of the pharma sector was less than a half billion dollars.

Penicillin had not been invented.

Insulin was extracted from pig bladders.

A leading treatment for mental disorders was lobotomy.

U.S. consumers spent less than 5% of their income on healthcare and less than 1% of their income on pharmaceuticals.

Merck and Wyeth were small chemical companies in New Jersey. Pfizer was making progress in confectionery.

J&J was building market leadership in Band-Aids. Some Lilly labs closed for the winter.

Eli Lilly worker operating machine for producing insulin by grinding pig pancreases.

Global Pharmaceutical sales exceed $1 trillion (by just how much we are going to discuss).

The value of the sector is over $5 trillion (up one thousand fold from the 1920s).

Mortality rates from major diseases including heart disease, cancer and stroke are down dramatically.

Most drugs on the market in developed economies have proven efficacy and safety.

U.S. consumers spent nearly a fifth of their income on healthcare and more than 3% of their income on pharmaceutical products.

The pharmaceutical business has globalized with modern drugs available in most countries in the world.

U.S. Pharma Spend Has Risen Rapidly in Real Terms

Pharmaceutical Expenditures in the U.S. Have Gone Up by 900 Times Since 1929.

INDEXED TOTAL PHARMACEUTICAL SPENDING ON AN INFLATION ADJUSTED BASIS, 1929–2016 (INDEXED 1929 = 100)

Acceleration of spending started in the 1990s with the advent of new medicines for chronic conditions and advanced medicines for cancer and expansion of employer-provided health insurance plans.

Pharmaceutical Sector Will Likely Triple in Size in the Next 50 Years
Healthcare Spending Rises with GDP

Healthcare Spending in the US Has Gone Up Faster than GDP Over The Last 90 Years

US GDP VERSUS TOTAL MEDICAL CARE SPENDING ON AN INFLATION ADJUSTED BASIS, 1929-2016

- Healthcare has an income elasticity of demand above one.
- Or put another way, once the consumer has covered the basics of food, shelter and transportation he directs the marginal consumption dollar to superior goods such as investment in life extension (medical care).
- Economists would call healthcare a "luxury good".

Source: Bureau of Economic Analysis, National Income and Product Accounts.
Pharma Spending Also Rises Disproportionately with Total Consumption

U.S. Pharmaceutical Spending in the US Has Gone Up Faster than Total Consumption Over The Last 90 Years

The percentage of the consumer’s wallet that is spent on pharma products has gone up dramatically since 1930.

The proportion of total spending that goes to pharmaceutical products has been rising at an increasing rate since 1990. This likely reflects acceleration of innovation, the advent of more expensive drugs for life threatening diseases, particularly biologics and the greater availability of employer and government reimbursement for pharmaceutical product expenditures.

Source: Bureau of Economic Analysis, National Income and Product Accounts.
Pharma Spending as a Fraction of Total Spend has Risen *Five Times in Less than a Century*

US Pharmaceutical Spend as a Percent of Total Consumer Spending, 1930-2016

- 1930: 0.71%
- 1940: 0.84%
- 1950: 0.78%
- 1960: 1.05%
- 1970: 1.13%
- 1980: 1.07%
- 1990: 1.54%
- 2000: 2.33%
- 2010: 3.23%
- 2016: 3.80%

There is a strong positive relationship between Pharma Expenditures / Capita in 2016 and GDP / Capita in the same year.

This cross-sectional pattern is consistent with the longitudinal data from the United States.

Globally, consumers spend an increasing fraction of their income on pharmaceuticals as their income rises up to GDP / Capita of $30,000 and then pharma spend rises roughly one to one with GDP afterwards.

On average pharma spend as a percent of GDP is 1.33% across 37 countries.

Source: OECD Health Data and Selected Country Level Sources; Torreya calculations.
GDP Growth Forecasts, Top 20 Countries, OECD

<table>
<thead>
<tr>
<th>Country</th>
<th>2017-2030</th>
<th>2030-2060</th>
</tr>
</thead>
<tbody>
<tr>
<td>World</td>
<td>3.7</td>
<td>2.3</td>
</tr>
<tr>
<td>USA</td>
<td>2.3</td>
<td>2.0</td>
</tr>
<tr>
<td>China</td>
<td>6.6</td>
<td>2.3</td>
</tr>
<tr>
<td>Japan</td>
<td>1.2</td>
<td>1.4</td>
</tr>
<tr>
<td>Germany</td>
<td>1.3</td>
<td>1.0</td>
</tr>
<tr>
<td>Russia</td>
<td>3.0</td>
<td>1.3</td>
</tr>
<tr>
<td>France</td>
<td>2.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Italy</td>
<td>1.3</td>
<td>1.5</td>
</tr>
<tr>
<td>Mexico</td>
<td>3.4</td>
<td>2.7</td>
</tr>
<tr>
<td>UK</td>
<td>1.9</td>
<td>2.2</td>
</tr>
<tr>
<td>Canada</td>
<td>2.1</td>
<td>2.3</td>
</tr>
<tr>
<td>South Korea</td>
<td>2.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Spain</td>
<td>2.0</td>
<td>1.4</td>
</tr>
<tr>
<td>Brazil</td>
<td>4.1</td>
<td>2.0</td>
</tr>
<tr>
<td>Australia</td>
<td>3.1</td>
<td>2.2</td>
</tr>
<tr>
<td>Poland</td>
<td>2.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>4.2</td>
<td>2.4</td>
</tr>
<tr>
<td>India</td>
<td>6.7</td>
<td>4.0</td>
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<tr>
<td>Argentina</td>
<td>3.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Indonesia</td>
<td>5.3</td>
<td>3.4</td>
</tr>
<tr>
<td>South Africa</td>
<td>3.9</td>
<td>2.5</td>
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</tbody>
</table>

Between now and 2060 (43 years), World GDP is expected to more than triple in real (inflation-adjusted) terms.

### Forecast “Real” Pharmaceutical Sector Growth

<table>
<thead>
<tr>
<th>Country</th>
<th>Size of Sector in Future Versus Size Today (Percentwise)</th>
<th>Pharmaceutical Expenditures (Current $millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2030 vs. 2017</td>
<td>2060 vs. 2017</td>
</tr>
<tr>
<td>World</td>
<td>160%</td>
<td>317%</td>
</tr>
<tr>
<td>USA</td>
<td>134%</td>
<td>243%</td>
</tr>
<tr>
<td>China</td>
<td>230%</td>
<td>454%</td>
</tr>
<tr>
<td>Japan</td>
<td>117%</td>
<td>177%</td>
</tr>
<tr>
<td>Germany</td>
<td>118%</td>
<td>159%</td>
</tr>
<tr>
<td>Russia</td>
<td>147%</td>
<td>216%</td>
</tr>
<tr>
<td>France</td>
<td>129%</td>
<td>196%</td>
</tr>
<tr>
<td>Italy</td>
<td>118%</td>
<td>185%</td>
</tr>
<tr>
<td>Mexico</td>
<td>154%</td>
<td>343%</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>128%</td>
<td>245%</td>
</tr>
<tr>
<td>Canada</td>
<td>131%</td>
<td>259%</td>
</tr>
<tr>
<td>South Korea</td>
<td>141%</td>
<td>191%</td>
</tr>
<tr>
<td>Spain</td>
<td>129%</td>
<td>196%</td>
</tr>
<tr>
<td>Brazil</td>
<td>169%</td>
<td>305%</td>
</tr>
<tr>
<td>Australia</td>
<td>149%</td>
<td>286%</td>
</tr>
<tr>
<td>Poland</td>
<td>140%</td>
<td>188%</td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>171%</td>
<td>348%</td>
</tr>
<tr>
<td>India</td>
<td>232%</td>
<td>754%</td>
</tr>
<tr>
<td>Argentina</td>
<td>158%</td>
<td>304%</td>
</tr>
<tr>
<td>Indonesia</td>
<td>196%</td>
<td>534%</td>
</tr>
</tbody>
</table>

**Source:** Torreya forecast based on OECD GDP projections and historical relationship between country GDP growth and pharmaceutical consumption.
Pharma Sector Outlook:

The pharmaceutical sector is likely to triple in size between now and 2060 after adjusting for inflation. This is a result of greater wealth – which in turns fuels society’s ability to pay for new drugs.
Total Value of the Pharmaceutical Sector Today over $5 Trillion

What is the Size and Composition of the Pharmaceutical Sector?
Torreya’s Data Group Tracks Global Pharma Sector

- Torreya is a globally active investment bank focused on the pharmaceutical sector.
- In the process of closing 150+ licensing, M&A and capital markets transactions in the last decade, we have had to learn the various players pharmaceutical sector in detail.
- We began to track assets, people and companies the industry with our own databases in 2008.
- Today, we have a dedicated data group which focuses on our internal database resources.
- Torreya’s data group is headed by Dr. Megan Ledger, a social statistician.
Torreya Pharma Study Approach

- Identified approximately 30,000 companies globally that are involved in doing research or marketing pharmaceutical products.
- Excluded OTC, distributors, manufacturing and API players from this database.
- Because over half the companies are not listed on a stock market, we developed an algorithm to impute value for private companies (based on financial metrics where available). Our approach is to use publicly traded company multiples in six key categories and to impute private company value.
- Collated a list of the top 2000 companies by value.

Note: All references to pharmaceutical company “Value” in the following pages refer to either enterprise value (market capitalization less cash plus debt) or, for private companies, values derived from our algorithm.
### Current Estimates of Industry Size by Net Revenue:

Recent estimates of the size of the global pharma sector in 2016 range from $774 billion to $868 billion.*

Torreya’s Estimate of Industry Size: $1.13 Trillion (30% larger than the previous estimate).

This estimate is the sum of net sales of the largest 1,700 companies in the pharmaceutical sector.

One of the key explanations of the difference is China and India. Torreya’s database likely goes deeper into ranks of Chinese and Indian pharmaceutical companies than other sources.

Our database is still likely missing some players so the actual revenue of the pharma sector is likely even higher than our estimate, although we have included some companies which have some non-pharma revenue in the compilation.

Pharma Sector is one of the Largest in the Global Economy

The value of the commercial side of the drug sector is approximately $5.4 trillion (about $700 per every living person).

Pharma is a very large and complex growing part of the global economy.

The only parts of the economy that are larger by value are technology, consumer products and oil.

The $5.4 trillion value estimate is calculated as the sum of the values of the top 2000 pharmaceutical companies in Torreya’s pharma database.
The world pharmaceutical sector value pie is led by 17 large global pharmaceutical companies (45% value share), followed by 277 smaller pharma companies (we call specialty pharma, 23% share), followed by China and the generic sector which are about the same in size. These are followed by Japan Pharma (6%) and Biotechnology (3%).

* We know the biotech sector seems smaller than some might have expected. This is because we classify a company with no approved product as a “biotechnology company” and a company with a marketed product that is not a big pharma, not a Japan pharma nor a China pharma as a specialty pharma company. Thus, many companies (think Incyte) that some would think of as biotech are classified by us as specialty pharma.
Value Evolution of the Top Twenty Companies Over Time

The global pharmaceutical industry has grown enormously in just six years by value. In August 2011 the value of the top 20 companies was $1.45 billion. Today, the top 20 companies are now worth $2.9 billion.

Global Value Champions

Up 351% with minimal M&A. Highly innovative cancer products.

Johnson & Johnson
Up $201 billion in value (equivalent to a whole large pharma). Introduction of numerous new high value biologics.
What Key Trends Will Shape the Pharmaceutical Sector?

Pharma Will Be Impacted by Cost Controls, Growth in Rare Disease Drugs and China
First Trend

Cost Controls Increase in Severity
As the pharmaceutical industry has grown, governments around the world have become more conscious of associated costs.

In more countries than not, pharmaceutical cost controls set by government reimbursement agencies have affected the direction and profitability of the pharmaceutical industry.

In free market economies, an increasing percentage of consumers’ budget is spent on pharmaceuticals as income grows. This pattern has held in the U.S.

However, because pharmaceutical spending is influenced to a significant degree by governmental decisions and associated budgets, the pattern between income and pharmaceutical spend has been broken in some markets – particularly in Europe.
# Examples of Global Drug Cost Containment Policies

<table>
<thead>
<tr>
<th>Policy Class</th>
<th>Specific Type of Action</th>
<th>Representative Countries Adopting Policy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pricing Controls and Cuts</td>
<td>One-off cut in prices of patented medicines</td>
<td>Austria, Belgium, Germany, Italy, Portugal, Spain, UK</td>
</tr>
<tr>
<td>Implementation of reference pricing</td>
<td>Brazil, Canada, France, Germany, Italy, Mexico, N. Zealand, Spain</td>
<td></td>
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<tr>
<td>Change in reference price system by cluster</td>
<td>Greece, Ireland, Portugal, Spain</td>
<td></td>
</tr>
<tr>
<td>Reduction of Mark-Up for Distributors</td>
<td>Austria, Canada, Greece, Ireland, Italy, Portugal, Spain</td>
<td></td>
</tr>
<tr>
<td>Implementation of Essential Drug List with Low Prices</td>
<td>Argentina, China, India, Russia, Vietnam</td>
<td></td>
</tr>
<tr>
<td>Mandatory Annual Price Cuts</td>
<td>Japan, Philippines</td>
<td></td>
</tr>
<tr>
<td>Increase of government rebates / most favored nation approach</td>
<td>Germany, United States</td>
<td></td>
</tr>
<tr>
<td>Extraordinary Price Reviews</td>
<td>Greece, Ireland, Portugal, Slovakia, Spain</td>
<td></td>
</tr>
<tr>
<td>Group purchasing approach / negotiation for lower prices</td>
<td>Canada</td>
<td></td>
</tr>
<tr>
<td>Reimbursement Policies</td>
<td>Delisting of products on reimbursement lists</td>
<td>Czech Republic, Greece, Portugal, Spain</td>
</tr>
<tr>
<td>Increase in patient co-pays</td>
<td>Austria, France, Greece, Ireland, Sweden</td>
<td></td>
</tr>
<tr>
<td>Health Technology Assessment / Cost-Benefit for price decisions</td>
<td>Germany, United Kingdom</td>
<td></td>
</tr>
<tr>
<td>Entry management agreement</td>
<td>Belgium, Italy, United Kingdom</td>
<td></td>
</tr>
<tr>
<td>Policies to promote generic medicines</td>
<td>Implementation of INN name prescribing (can't use brand name)</td>
<td>France, Italy, Portugal, Slovakia, Spain</td>
</tr>
<tr>
<td>Incentives for physicians to prescribe generics</td>
<td>Belgium, France, Hungary, Japan</td>
<td></td>
</tr>
<tr>
<td>Incentives for pharmacists to prescribe generics</td>
<td>Belgium, France, Ireland, Japan</td>
<td></td>
</tr>
<tr>
<td>Incentives for patients to receive generics</td>
<td>France, Iceland, Ireland, Portugal, Spain</td>
<td></td>
</tr>
<tr>
<td>Generic price cuts and tendering approach</td>
<td>Canada, China, Italy, Vietnam</td>
<td></td>
</tr>
</tbody>
</table>

Real Pharma Spend Dropped in Almost All European Countries After 2009

Government-mandated price reductions have led to substantial declines in real pharmaceutical spending after 2009 in countries such as Portugal, Denmark, the Netherlands and Spain.

Retail Pharmaceutical Spending Growth Before and After 2009 in Real Terms, OECD Countries

Europe spends about 40% less than the US as a percentage of GDP on drugs. Remarkably, Europe also spends less on GDP-adjusted basis than Canada, Mexico, South Korea and even Russia.

Source: Torreya research and OECD data.
Case Study: Portugal

Portugal unfortunately found that its national debt became unsustainably high and sought a €79.0 billion IMF debt bailout in 2011. This was followed by deep budget cuts that were ultimately followed by an economic turnaround. In Portugal, there is a single default insurer for most drugs, the National Health Service. The *Infarmed* sets retail drug prices. Drug prices were cut by between 10% and 30% per annum in many years in the 2009-2015 time period. The result was that the average price of generic drugs fell by more than two thirds between 2003 and 2013 and branded drug prices were cut by roughly a third.

In an article, *Tough Times for Pharma in Portugal* on Dec 10, 2012 it was reported: “The approval of new drugs has ground to a halt for 18 months and reimbursement decisions have been constricted for non-generics says the Portuguese pharmaceutical industry body, Apifarma. Price cuts and mounting debt in public hospitals are making access to essential medicines more difficult for patients and harming the industry, it warns.” By 2013, Portugal’s drug prices mirrored those of Estonia and Slovakia.

The impact on the domestic pharmaceutical industry was devastating. Portugal’s leading domestic branded pharmaceutical company is Bial, led by Luis Portela. “Luis Portela mentioned in 2013 that Bial had to postpone the development of a new Parkinson´s Disease drug due to budget constraints.” [Pharmupdates, Mar 15, 2015].

Portugal cut drug prices to the levels seen in Estonia. The result was decreased access to drugs and significant hardship on the R&D efforts of local companies like Bial.
With the exception of the United States, all OECD countries directly regulate pharmaceutical prices.

In the United States pressure on pharmaceutical prices is becoming increasingly severe. The VA and State Medicaid receive substantial discounts in the United States as do hospitals and other providers who reach substantial amounts of low income recipients (340B program).

According to Blumenthal and Squires: “The strategies described above clearly result in cheaper drugs for the VA, DOD, Medicaid, and 340B providers. The Congressional Budget Office has estimated that the VA and DOD pay drug prices that are roughly half as much as those paid by retail pharmacies, and that Medicaid pays about one-third less than Medicare Part D (which pays whatever prices its plans negotiate in private markets). The agency that runs the 340B program estimates that it reduces drug prices for participating providers by one-third.”

In one recent study carried out by three authors from the London School of Economics*, it was noted: “This paper analyses the impact of reimbursement regulation on launch times in the adoption of new medicines in a sample of OECD countries and a subsample of European countries. The latter also allows examination of price spillover effects, given that pharmaceutical product reimbursement regulation commonly benchmarks from prices in other countries. We empirically focus on the relative delays imposed by regulation on the adoption of a global set of molecules, which have diffused across more than 10 markets in the OECD over the period 1999–2008, controlling for various confounding effects. Through examining time to launch across a number of markets, and controlling for a number of confounding influences, we find that price and reimbursement regulations appear to delay the adoption of new pharmaceutical products. We also find that the existence of interdependencies in pricing may have a further indirect effect of such regulation on launch times. Firm economies of scale, the therapeutic importance of specific product innovations and market size are found to counter the delaying impact of price and reimbursement regulation on new medicines adoption.”

In 2004, the U.S. Department of Commerce published a study of the impact of OECD price controls on the global pharmaceutical industry. The study noted that OECD price controls could be linked to reductions in global R&D spending of approximately $5 to $8 billion per year with the consequence of 3 to 4 new molecular entities not being developed per annum. These NME’s would have had many billions of benefit for consumers according to HHS analysis.
Second Trend

Greater Focus on Rare Disease
The 1983 Orphan Drug Act in the U.S. was designed to encourage drug manufacturers to develop new medicines for smaller, neglected diseases that didn't offer as much of a financial return.

Along with tax credits and other benefits, the 1983 law granted drugmakers who secured approval of a rare disease drug seven years of marketing exclusivity — a powerful monopoly. Later, certain orphan disease developers also received the right to FDA Priority review vouchers.

Other countries have also adopted incentives to develop drugs for rare disease.

As a result, developing drugs for rare disease has become increasingly mainstream.

Because of low development costs but high market value, this area has attractive substantial investment.
We identified a number of pure play rare disease companies and have also included the Genzyme segment of Sanofi. Rare disease therapeutics companies have themselves gone from being a rarity to an important and growing part of the pharmaceutical marketplace. In October 2017, the total enterprise value of the top 20 pure play rare disease non-oncology companies was $315 billion. Many oncology companies have pursued rare forms of cancer for approvals. The sum of the enterprise value of pure play rare disease oncology companies as of October 2017 was $193 billion. The end result is that the pure play segment of rare disease is now more than a half trillion in value. To be sure, some of the rare disease companies counted here have products that are not aimed at the orphan market (e.g., Shire’s ADHD franchise). However, since many big pharmas (not counted here) also have rare disease products in their portfolio, the real value of the rare disease segment of the pharma industry is likely much higher overall than the half trillion mark noted here. However, one looks at it, the rare disease segment of the pharma sector is one of the largest and likely to remain so.
Value of Rare Disease Sector is Up Thirteen Times Since 2000

TOTAL ENTERPRISE VALUE ($MIL) OF TOP 31 PURE PLAY RARE DISEASE THERAPEUTIC COMPANIES

(INCLUDED ARE GENZYME AND ASSUMED VALUE OF GENZYME TODAY. ALSO INCLUDED IS BAXALTA BACK TO 2000 USING ASSUMPTIONS ON VALUE UNDER BAXTER FROM 2000-2014).

Source: Torreya calculations using data obtained CapitalIQ, October 2017.
The pure rare disease sector is now more than 17% of the value of the big pharma sector - larger than the entire biotech sector (defined as the value of companies that do not yet have an approved drug) and larger than the entire Japan pharma sector or China pharma sector.

This estimate belies even greater value because substantial portions of non-pure play big pharma (e.g., BMS, Merck, Novartis) are now driven by rare disease drugs.

### Top Pure Play Rare Disease Companies by Value ($millions)

#### FYE Enterprise Value of Leading Pure Players in Rare Disease Therapeutics, 2000 – 2017

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Biogen</td>
<td>Multiple Sclerosis</td>
<td>$3,548</td>
<td>$11,303</td>
<td>$14,459</td>
<td>$90,507</td>
<td>$62,236</td>
<td>$69,812</td>
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<tr>
<td>Shire (predecessors)</td>
<td>Hereditary Angioedema</td>
<td>$16,572</td>
<td>$18,563</td>
<td>$33,788</td>
<td>$71,017</td>
<td>$59,590</td>
<td>$67,777</td>
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<tr>
<td>Vertex Pharma</td>
<td>Cystic Fibrosis</td>
<td>$1,900</td>
<td>$769</td>
<td>$7,032</td>
<td>$26,938</td>
<td>$20,965</td>
<td>$37,428</td>
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<tr>
<td>Genzyme</td>
<td>Multiple Sclerosis</td>
<td>$4,062</td>
<td>$14,813</td>
<td>$14,653</td>
<td>$28,391</td>
<td>$31,250</td>
<td>$36,070</td>
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<tr>
<td>Alexion</td>
<td>Paroxysmal Nocturnal Hemoglobinuria</td>
<td>$1,604</td>
<td>$720</td>
<td>$4,177</td>
<td>$33,707</td>
<td>$33,572</td>
<td>$33,114</td>
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<tr>
<td>BioMarin</td>
<td>Morquio Syndrome</td>
<td>$1,173</td>
<td>$382</td>
<td>$2,219</td>
<td>$16,966</td>
<td>$13,299</td>
<td>$16,261</td>
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<tr>
<td>Jazz Pharma</td>
<td>Narcolepsy</td>
<td></td>
<td>$472</td>
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<td>$11,342</td>
<td>$7,675</td>
<td>$10,141</td>
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<tr>
<td>Biorverativ</td>
<td>Hemophilia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$6,086</td>
</tr>
<tr>
<td>Ionis Pharma</td>
<td>Spinal Muscular Atrophy</td>
<td>$570</td>
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<td>$467</td>
<td>$7,598</td>
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<td>$6,053</td>
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<tr>
<td>bluebird bio</td>
<td>Cerebral Adrenoleukodystrophy</td>
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<td>$2,663</td>
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<td>$1,320</td>
<td>$5,320</td>
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</tr>
<tr>
<td>United Therapeutics</td>
<td>Pulmonary Arterial Hypertension</td>
<td>$1,296</td>
<td>$945</td>
<td>$3,156</td>
<td>$6,672</td>
<td>$4,713</td>
<td>$4,225</td>
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<tr>
<td>Swedish Orphan Biovitrum</td>
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<td>$3,100</td>
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<td>$4,073</td>
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<tr>
<td>Horizon Pharma</td>
<td>Urea Cyclic Disorders</td>
<td></td>
<td>$2,695</td>
<td></td>
<td>$3,029</td>
<td>$3,409</td>
<td></td>
</tr>
<tr>
<td>Spark Therapeutics</td>
<td>Retinal Dystrophy</td>
<td></td>
<td>$1,627</td>
<td></td>
<td>$634</td>
<td>$3,044</td>
<td></td>
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<tr>
<td>AveXis, Inc.</td>
<td>Spinal Muscular Atrophy</td>
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<td></td>
<td></td>
<td>$500</td>
<td>$2,671</td>
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<tr>
<td>Amicus Therapeutics</td>
<td>Fabry Disease</td>
<td></td>
<td>$17</td>
<td>$674</td>
<td>$599</td>
<td>$2,416</td>
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<tr>
<td>Concept Therapeutics</td>
<td>Cushing's Syndrome</td>
<td>$60</td>
<td>$152</td>
<td>$415</td>
<td>$416</td>
<td>$2,127</td>
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<tr>
<td>Prothena Corporation</td>
<td>AA Amyloidosis</td>
<td></td>
<td>$492</td>
<td></td>
<td>$765</td>
<td>$2,060</td>
<td></td>
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<tr>
<td>Ultragenyx</td>
<td>X-Linked Hypophosphatemia</td>
<td></td>
<td>$1,826</td>
<td></td>
<td>$1,991</td>
<td>$1,970</td>
<td></td>
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<tr>
<td>Intercept Pharma</td>
<td>Primary Biliary Colangitis</td>
<td></td>
<td>$4,866</td>
<td></td>
<td>$2,082</td>
<td>$1,624</td>
<td></td>
</tr>
</tbody>
</table>

| Subtotal Value ($millions)   |                                     | $30,725    | $47,929    | $81,698    | $311,493   | $252,231   | $315,681   |

#### Oncology

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Celgene</td>
<td>Multiple Myeloma</td>
<td>$1,883</td>
<td>$5,125</td>
<td>$24,562</td>
<td>$85,514</td>
<td>$113,055</td>
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<tr>
<td>Incyte</td>
<td>Myelofibrosis</td>
<td>$3,875</td>
<td>$539</td>
<td>$1,371</td>
<td>$13,452</td>
<td>$12,709</td>
<td>$23,576</td>
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<td>Genmab</td>
<td>Chronic Lymphocytic Lymphoma</td>
<td>$158</td>
<td>$406</td>
<td>$506</td>
<td>$3,713</td>
<td>$5,857</td>
<td>$13,477</td>
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<tr>
<td>Kite Pharma</td>
<td>Diffuse B Cell Lymphoma</td>
<td></td>
<td></td>
<td></td>
<td>$2,088</td>
<td>$1,569</td>
<td>$9,533</td>
</tr>
<tr>
<td>Exelixis</td>
<td>Advanced Renal Cell Carcinoma</td>
<td>$703</td>
<td>$486</td>
<td>$544</td>
<td>$4,193</td>
<td>$3,609</td>
<td>$7,773</td>
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<tr>
<td>Seattle Genetics</td>
<td>Relapsed Hodgkin's Lymphoma</td>
<td>$172</td>
<td>$926</td>
<td></td>
<td>$823</td>
<td>$1,045</td>
<td>$7,207</td>
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<tr>
<td>Tesaro</td>
<td>Ovarian Cancer</td>
<td></td>
<td></td>
<td></td>
<td>$1,744</td>
<td>$1,521</td>
<td>$6,122</td>
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<tr>
<td>Juno Therapeutics</td>
<td>Relapsed B-Cell Non-Hodgkins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$4,961</td>
<td>$2,605</td>
</tr>
<tr>
<td>Clovis Oncology</td>
<td>Lymphoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$4,182</td>
</tr>
<tr>
<td>Array BioPharma</td>
<td>Advanced Ovarian Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$2,406</td>
<td>$466</td>
</tr>
<tr>
<td>Loxo Oncology</td>
<td>BRAF-mutant Melanoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$3,755</td>
</tr>
<tr>
<td></td>
<td>Solid tumors with NTRK-fusion proteins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$704</td>
<td>$474</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$2,307</td>
<td></td>
</tr>
</tbody>
</table>

| Subtotal Value               |                                     | $6,619     | $6,728     | $27,909    | $132,310   | $115,595   | $193,116   |
| Total Value                  |                                     | $37,344    | $54,657    | $109,607   | $445,803   | $367,826   | $508,797   |
| Value as Percent of Big Pharma Value |                                 | 2.75%      | 3.98%      | 7.58%      | 16.36%     | 14.63%     | 17.54%     |

Source: Torreya calculations using data obtained CapitalIQ, October 2017.
We collected data on prevalence of the leading diseases treated by the top 20 rare disease companies listed on the previous page (see table at right). The known prevalence data are often incomplete and can be off substantially. Recall that the sum of the enterprise value of these companies is $315 billion. It is important to note that these companies offer drugs that treat more than just these diseases.

The collective prevalence of the leading diseases treated by these rare disease companies is 300 per 100,000 or 0.3%. Assuming that the drugs developed by these companies reach all of the world’s population, the number of persons treated would be under 25 million. To put it in perspective, somewhere between 10% and 20% of the world’s pharmaceutical sector value is associated with treatments for well less than 1% of the world’s population.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Prevalence per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple Sclerosis</td>
<td>90</td>
</tr>
<tr>
<td>Hereditary Angioedema</td>
<td>2</td>
</tr>
<tr>
<td>Cystic Fibrosis</td>
<td>25</td>
</tr>
<tr>
<td>PNH</td>
<td>0.16</td>
</tr>
<tr>
<td>Morquio</td>
<td>0.16</td>
</tr>
<tr>
<td>Narcolepsy</td>
<td>50</td>
</tr>
<tr>
<td>Hemophilia</td>
<td>20</td>
</tr>
<tr>
<td>Spinal Muscular Atrophy</td>
<td>13</td>
</tr>
<tr>
<td>Cerebral Adrenoleukodystrophy</td>
<td>3</td>
</tr>
<tr>
<td>Pulmonary Arterial Hypertension</td>
<td>3</td>
</tr>
<tr>
<td>Urea Cycle Disorders</td>
<td>3</td>
</tr>
<tr>
<td>Retinal Dystrophy</td>
<td>13</td>
</tr>
<tr>
<td>Fabry Disease</td>
<td>30</td>
</tr>
<tr>
<td>Cushing's Syndrome</td>
<td>1</td>
</tr>
<tr>
<td>AA Amyloidosis</td>
<td>1.5</td>
</tr>
<tr>
<td>X-Linked Hypophosphatemia</td>
<td>5</td>
</tr>
<tr>
<td>Primary Biliary Colangitis</td>
<td>40</td>
</tr>
</tbody>
</table>

Total 299.8

Source: various reports on prevalence of individual diseases.
We See Continued Growth in Rare Disease Sector

Given the statistics shown on the previous page, one might suspect that we will see a slowdown in the rare disease sector in the future. We do not believe that this is a likely outcome for several reasons:

1. Rare disease companies are making a difference for patients. Most of the treatments sold by these companies are truly life-saving and extend life substantially.

2. Reimbursement favorable in wealthy countries and likely to become more favorable. Budgets are available in many countries to pay for rare disease drugs.

3. Rare disease business is globalized and less vulnerable to reimbursement changes in any one country.

4. Strong patient advocacy groups underlie government’s willingness to reimburse rare disease drugs.

5. Number of new drugs in development rising fast and likely to continue on the same path. We are still relatively early in finding cures for many genetic diseases.

6. The pipeline is rich and is benefitting from breakthroughs in gene therapy, nucleic acid therapy and gene editing.
We have discussed substantial price cuts made by European and Asian governments worldwide, especially following the Global Financial Crisis. Interestingly, the same governments that have implemented severe price cuts have been relatively permissive about pricing and reimbursement for rare disease drugs. The table above shows the market reality which is that there is little discounting across countries of rare disease products like Kalydeco or Soliris.

This is a reflection of the profound impact that these drugs can make on the lives of patients that are treated and the rarity of the diseases treated. The overall budgetary burden of rare disease drugs has been modest thus far. Europe, Latin America, Japan and North America have taken relatively permissive policies towards rare disease drugs. In contrast, the two most populous countries – China and India have not adopted orphan drug regulation and associated pricing policies.

It is important to note that there are often value limits imposed on the potential sales of a rare disease drug by a country and it is not uncommon for rebates to be put in place to lower the effective cost.
The interest in marketing rare disease drugs has risen markedly in recent years. This has been associated with policies from the Japanese MHLW that encourage sales of such drugs. Pricing is generally within 70% to 120% of the global prevailing price.

Recently, Japan’s MHLW expanded orphan drug criteria from diseases with less than 50,000 patients to less than 180,000 patients if the disease is classified as an otherwise “intractable disease”.

Japanese regulators also introduced the “ultra-expensive drug repricing rule” in early 2016 that allowed for drug prices to be slashed if they exceeded revenue forecasts provided at the initial approval. This was in reaction to the high pricing of Opdivo in Japan. To date, this rule has yet to be implemented.
Reimbursement policies are favorable towards rare disease drugs in many countries. Thus, despite high prices for many rare disease drugs, the distribution of these drugs is highly globalized. For most countries, the cost of these drugs has yet to raise substantial budgetary concerns in comparison to rising costs for other drug categories (e.g., cancer care, autoimmune disease, diabetes). To illustrate the globalization of rare disease drugs, consider the sales distribution charts below taken from the 2016 annual reports of Alexion and BioMarin – two leading pure play rare disease companies. Alexion’s revenues are 36% from the US and BioMarin’s 46%. These figures are in line with the current global distribution of pharma sales.
Orphan Drug Designation Requests at FDA Have Doubled in the Last Five Years

Number of Orphan Drug Designation Requests Received by FDA's Office of Orphan Drug Development, 2012-2016

Source: FDA Orphan Drug Modernization Plan, June 29, 2017.
A key advance in the last forty years in science has been the decoding of the genome and the increasing understanding of the genetic causes of rare disease.

The last decade has seen widespread advances in the ability to use drugs to address genetic mutations and associated disease.

Particularly exciting has been the application of nucleic acid therapeutics by companies such as Alnylam and Ionis for rare disease. More recently, we have seen rapid advances made with gene therapy and gene editing as a mechanism to address genetic diseases.

Companies such as AveXis, AVROBIO, bluebird, Editas and Spark Therapeutics have made major advances in gene therapies and editing for rare disease. We expect the pace of innovation from such companies to accelerate in the years ahead.

Ultragenyx Acquisition

Dimension Therapeutics uses (AAV) gene delivery technology to develop rare disease therapeutics. Dimension has drugs in Phase 1/2 development inherited metabolic diseases, including OTC deficiency and GSD1a.

Traditionally, strategic players in rare disease have avoided investment and M&A in gene therapy – seeing this area as quite risky.

Ultragenyx’s acquisition of Dimension in October 2017 for $150 million is a landmark transaction in rare disease therapeutics insofar as it represents one of the first times where there has been high acquisition in a gene therapy company.
Third Trend

Growing Importance of China
Chinese Pharmaceutical Market Growth

Total Pharma Revenues, China 2005-2017, ($ Billions)

Key Trends

- Chinese pharmaceutical market has grown six times larger in just 13 years
- China is the second largest pharma market in the world today
- Usage of Western medicines up massively
- High growth for cancer, cardiovascular, and respiratory drugs given disease burden in the Chinese population

Source: OECD Estimates
Growing Importance of Chinese Pharmaceutical Sector

Chinese companies have added $84 billion in shareholder value in just 18 months. This is despite major changes in the regulatory regime and increasing pressure on prices (especially via Essential Drug Lists).

Valuation of the Leading Chinese Private and Publicly-Traded Pharmaceutical Companies, Last 18 Months

<table>
<thead>
<tr>
<th>Company</th>
<th>Value Rank</th>
<th>Value Estimate ($ mil)</th>
<th>2016 Revenue ($mil)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yangtze River Pharma</td>
<td>1</td>
<td>$ 50,630</td>
<td>$ 8,300</td>
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<tr>
<td>Hengrui</td>
<td>2</td>
<td>$ 22,391</td>
<td>$ 1,606</td>
</tr>
<tr>
<td>CR Pharma Rx Segment</td>
<td>3</td>
<td>$ 19,087</td>
<td>$ 3,129</td>
</tr>
<tr>
<td>Qilu Pharma</td>
<td>4</td>
<td>$ 16,520</td>
<td>$ 1,666</td>
</tr>
<tr>
<td>Kangmei Pharma</td>
<td>5</td>
<td>$ 15,239</td>
<td>$ 3,159</td>
</tr>
<tr>
<td>Yunnan Baiyao</td>
<td>6</td>
<td>$ 13,505</td>
<td>$ 3,245</td>
</tr>
<tr>
<td>Fosun Pharma</td>
<td>7</td>
<td>$ 12,275</td>
<td>$ 2,125</td>
</tr>
<tr>
<td>Sinopharm - Rx Segment</td>
<td>8</td>
<td>$ 12,163</td>
<td>$ 1,994</td>
</tr>
<tr>
<td>CSPC Pharma</td>
<td>9</td>
<td>$ 9,252</td>
<td>$ 1,522</td>
</tr>
<tr>
<td>Huadong / China Grand</td>
<td>10</td>
<td>$ 6,863</td>
<td>$ 3,634</td>
</tr>
<tr>
<td>Tasly Pharma</td>
<td>11</td>
<td>$ 6,209</td>
<td>$ 2,017</td>
</tr>
<tr>
<td>Sino Biopharma</td>
<td>12</td>
<td>$ 6,097</td>
<td>$ 1,990</td>
</tr>
<tr>
<td>Neptunus Group</td>
<td>13</td>
<td>$ 5,831</td>
<td>$ 956</td>
</tr>
<tr>
<td>Chongqing Zhifei Bio</td>
<td>14</td>
<td>$ 5,765</td>
<td>$ 65</td>
</tr>
<tr>
<td>Kanghong Pharma</td>
<td>15</td>
<td>$ 5,038</td>
<td>$ 365</td>
</tr>
<tr>
<td>Salubris Pharmaceuticals</td>
<td>16</td>
<td>$ 5,010</td>
<td>$ 543</td>
</tr>
<tr>
<td>Kelun Pharma</td>
<td>17</td>
<td>$ 5,008</td>
<td>$ 1,241</td>
</tr>
<tr>
<td>Humanwell</td>
<td>18</td>
<td>$ 4,782</td>
<td>$ 1,784</td>
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<tr>
<td>Dongbao Pharma</td>
<td>19</td>
<td>$ 4,670</td>
<td>$ 286</td>
</tr>
<tr>
<td>GPC</td>
<td>20</td>
<td>$ 4,389</td>
<td>$ 2,939</td>
</tr>
</tbody>
</table>

Source: Torreya calculations and Torreya pharma database.
China Will Lead Major Market Growth in the Pharma Sector Over the Next 50 Years

US market will double while China market up 4X. Japan, Germany and France markets will grow less than 2X.

Source: Torreya calculations and OECD data.
China Passes W. Europe in Total Market Share by 2060

Current Share of Pharma Revenue by Country, 2017

- USA: 33%
- China: 10%
- Western Europe: 15%
- Latam: 7%
- ROW: 6%
- India: 1%
- Japan: 9%
- Russia: 4%
- Saudi Arabia: 1%
- Australia: 1%

Forecast Share of Pharma Revenue by Country, 2060

- USA: 30%
- China: 18%
- Western Europe: 17%
- Latam: 8%
- ROW: 5%
- India: 3%
- Russia: 3%
- Saudi Arabia: 2%
- Australia: 1%

Source: Torreya calculations and OECD data.
Implications for the Global Sector of China’s Rise

- If forecasts for outsize GDP growth in China in the decades ahead hold true it is highly likely that the China market will not only come to rival that of the United States but also outstrip the entire pharmaceutical sector in Europe.

- As already discussed, the European sector has increasingly been saddled by severe price controls – reflecting structural fiscal issues in the EU. By hampering GDP growth, Europe’s sector will collectively become increasingly less relevant in the global pharmaceutical sector.

- Japan is also destined to become a less relevant pharmaceutical marketplace in time given its slower GDP growth.

- The implications for the sector are obvious. Just as other sectors such as film have begun to tilt their product towards the taste of Chinese consumers, we will increasingly see the pharmaceutical industry address diseases which are particularly prevalent in China such as liver fibrosis, hepatitis, gastric cancer, etc.
6. What Innovations Could Change the Pharma Sector in the Future?

Innovations in Inflammation Control, Nucleic Acids and Implantables Will Transform Industry
First Innovation

Better Manufacture Will Facilitate Dramatic Growth in Peptide Therapeutics
“Peptide manufacturing can be achieved entirely through chemical synthesis, either in the solution phase (top left), coupled to a solid phase (top right) or by the combination of both. Alternatively, peptides can be produced by recombinant microorganisms (bottom left) or by extraction from their natural (plants or animal) source.”

Peptides Will be Increasingly Important in the Pharmaceuticals

Today, the peptide market is around $20 billion. In the future this market will likely double or triple.

However, the challenge is that new peptides are longer and much more difficult to make with Solid State Synthesis or recombinant methods.

Manufacturing is especially difficult for long peptides where impurities from SPS are show stoppers.
Manufacturing Innovation is Going to Change This Field

1. Enzymatic Synthesis of Peptides
2. Better Recombinant Production and Processing
A Company to Watch

Has patented methods for using enzymes to dramatically reduce the cost and complexity associated with manufacture of long peptides.

A major innovation given the primacy of solid state synthesis and recombinant manufacture in today’s peptide market.

New generations of peptides such as Semaglutide will be far easier and cheaper to make in the future.
Second Innovation

Control of Inflammation May Substantially Reduce Mortality from Cancer & Heart Disease
Inflammation Hypothesized by Dr. Paul Ridker to be a Key Cause of Heart Attacks

Inflammation is a Key Hallmark of Atherosclerosis, Potentially Leading to Heart Attacks and Death from Heart Disease. This motivated the Novartis CANTOS study, which looked at whether IL-1beta blockade with Canakinumab reduced the risk of cardiac events.
1. Substantial improvement in heart disease observed in persons treated with an IL-1beta antibody (Canakinumab). MACE (primary endpoint) was reduced by 15% over the 3.7 year median follow-up period.

2. A dose dependent reduction in cancer was seen in those persons treated with Canakinumab over four years.

3. At the highest dose in the trial (300mg Canakinumab), there was a 51% reduction in all cancer mortality versus placebo.

4. At the highest dose in the trial (300mg Canakinumab), there was a 77% reduction in lung cancer mortality versus placebo.

Source: Novartis Website, August 2017.
1. These are profound results with implications for the world population (heart disease and cancer are the two leading causes of mortality worldwide).

2. Novartis sponsorship of the trial carried out in collaboration with Dr. Ridker and others represents the first large-scale validation that control of inflammation can reduce cancer.

3. Novartis is likely to pursue approval of Canakinumab for cardiovascular disease prevention and cancer prevention.

4. The findings of this trial creates an important research agenda for companies focused on science and biologics as there is clearly much more to learn about the potential for inflammation control to impact cancer and heart disease.
Third Innovation

Nucleic Acid Therapeutics Will Grow the Pharmaceutical Field
Nucleic Acids Are Increasingly Being Developed as Therapeutics

Our genes (DNA or deoxyribonucleic acid) regulate protein expression which affects all aspects of our body through transcription of gene factors that are regulated by RNA (ribonucleic acid) and, ultimately, messenger RNA (mRNA).

We refer to the class of companies working with DNA delivery, DNA modification (gene editing, gene therapy) and modified RNA/mRNA as being involved in Nucleic Acid Therapeutics.

Some of the most exciting young biotech companies worldwide are in the field of nucleic acid therapeutics,

Three Exciting Young Companies

- Alnylam Pharmaceuticals
  - Using RNAi to prevent transcription of disease-causing proteins

- editas Medicine
  - Using CRISPR-cas9 gene editing to conquer disease

- Moderna
  - Delivering mRNA directly as a drug
The APOLLO trial enrolled 225 hATTR amyloidosis patients with polyneuropathy, representing 39 genotypes, at 44 study sites in 19 countries around the world. Patients were randomized 2:1 to patisiran or placebo, with patisiran administered intravenously at 0.3 mg/kg once every three weeks for 18 months. For both the mNIS+7 and Norfolk QOL-DN endpoint measures provided below, a lower score indicates a better clinical result.

At 18 months, the mean change from baseline in mNIS+7 was significantly lower in the patisiran group as compared with placebo (p less than 0.00001). The mean and median changes in mNIS+7 impairment scores for patisiran both achieved negative values, indicating an improvement overall and in the majority of patients compared with baseline.

Liver cirrhosis, as well as fibrosis in other organs, involves the formation of excess connective tissue. This process results in permanently scarred organs. Collagen is the key constituent of this excess connective tissue and in the liver the collagen is synthesized by hepatic stellate cells.

BMS/Nitto Denko are developing a drug for the treatment of fibrotic diseases of the liver and of other organs. The first clinical indication being tested is liver cirrhosis. Phase 1 clinical trials using ND L02-s0201, an siRNA lipid nanoparticle which targets hepatic stellate cells showed direct reduction of collagen production from liver cells in man.

There is a $20 billion market opportunity for the first company to cure liver fibrosis and cirrhosis.
In theory, a gene therapy product could produce a **one time correction** of a genetic mutation which would mean that a disease would not require additional treatment.

This is medically important but also of high economic interest given the cost burden of **chronic patients** with long-term pharmaceutical treatments.

**Gene editing** is a particularly promising approach to gene therapy. CRISPR /Cas9 genome editing can target virtually any gene location where there is a mutation that is the cause of a disease. CRISPR-Cas9 editing leverages the complex of nuclease protein and RNA guides to reprogram nuclease.

The first CRISPR products are now in **clinical testing** and appear to have high potential. It is also possible to edit large populations of mutated cells, with the result that edited cells can ultimately grow over time and overcome the burden of a mutation.
Genetically targeted drugs are not helpful if genetic mutations are not found in the first place.

Thanks to the introduction of rapid gene sequencing and, now, the advent of next generation sequencing (NGS) machines, it has become practical to sequence the genes of the broader population. Companies such as 23&Me are growing rapidly in the consumer genomics space and there is high growth taking place worldwide in the field of prenatal gene sequencing.

We expect substantial volume of NGS-guided medications to come to market in the decades ahead, including genetic marker-based drug choice, genetic background-guided disease care protocols, etc, which will lead to precision medicine and subsequent cost containment (by sparing waste of drug consumption).

Key companies that are driving NGS-guided medicine include Foundation Medicine (part of Roche) and Ambry (part of Konica Minolta).
Fourth Innovation

Cell Therapy is Becoming Mainstream in the Pharmaceutical Industry
The Growing Importance of Cell Therapy

- Cell therapy involves injection of cellular material into a patient for therapeutic benefit.
- Cell therapies have been approved clinical for many years. Genzyme pioneered Carticel for knees and Epicel for burns in the 1990s.
- Today, hundreds of cell therapy products are in clinical testing and the expected market for these products is likely to grow dramatically over the next decade.
- Key players in cell therapy today include Adaptimmune, Asterias, bluebird, Celgene, Cellectis, Kite, Mesoblast, Novartis, Osiris, Smith & Nephew, Tigenix and Vericel.
- There are hundreds of emerging companies that are making major investments to build a business in this field.
- Not so long ago, cell therapy was viewed as having little to do with the pharmaceutical industry. Today, attitudes have changed substantially.
With CAR-T being the first meaningful achievement, more T-cell mediated target therapy will follow as disease/marker specific cell-based modality particularly for end stage cancer and other life-threatening conditions.

Companies to look at in this area are Adaptimmune (with GSK), Noile Immune (with Takeda) and a future comer, Neon.

TCR technologies are rapidly maturing and companies like Adaptimmune, Kite and Lion Bio have meaningful libraries of TCRs.

We expect this area of pharmaceutical drug development to grow rapidly in the next decade.

Several groups such as Aleta Biotherapeutics are working to extend CAR-T cancer treatments to solid tumors.
“Cell therapy is the fastest growing segment of regenerative medicine. Cell therapy is comprised of immune cell therapy and stem cell therapy, with stem cell therapy making up the largest part of this market; it is estimated that the global stem cell therapy market will reach $40 billion by 2020 and $180 billion by 2030.”


“Current regenerative medicine market is worth $18.9 billion globally, and will hit over $53 billion by 2021.

According to the [Research and Markets] report ‘due to the dominance of the bone and joint reconstruction market, the US currently has the biggest space, followed by Europe. However, due to recent positive legislation in Japan and Europe, the stem cell arena will grow more substantially in these regions over the next five years. By 2021, it is possible that Europe will surpass the US market with respect to stem cell applications, and this will become more likely if the Trump Administration restricts legislation and funding.”

Fifth Innovation

Implantables and Electroceuticals Will Redefine Therapeutic Sector
The human body can be thought of as an electronic device which can be measured and modulated.

The future will involve electroceuticals: electronic intervention of/in the nervous system.

One key idea advanced by GSK and their joint venture with Google called Galvani Bioelectronics is to use miniature devices that change nerve electrical signals to address disease:

- Strong prior evidence that this approach works for a number of diseases
- Technology is at the point where this approach is feasible
- Potential for revolutionary change in medicine – could be quite disruptive
- The associated area of Brain Machine Interface (BMI) also receiving substantial investment
The future will involve implantables that monitor the body and deliver drugs when needed.

Sensing microprocessors monitor and treat your body before you know you need treatment.

We believe that medicine will be changed profoundly by implantable systems that deliver pharmaceutical products on demand.

A second idea advocated by Medtronic and others is that digital technologies and endogenous sensors can facilitate the creation of digitally-enabled pharmaceutical drug/device combinations where the innovation is around the drug not in the drug itself. In particular, Medtronic has developed closed loop systems where drug dosing is automatically controlled endogenously. Groups like Baxter and Qualcomm recognize the potential to radically change hospital and subacute care and are racing to innovate.
Both Ideas Are Enabled by Advances in Electrical Engineering and Digital Technology

Better sensors
Extreme miniaturization of electronics
Advances in ASIC (application specific integrated circuits)
Advances in FPGA’s (field programmable gate arrays)

Digital Technology Also Important

Big data / inexpensive analytics
Sharing of data using TCP/IP
GSK’s Bioelectronics Initiative

From GSK Web Site (May 2017)

• Bioelectronic medicine is a vision far from today’s medical practice. But we believe that one day, tiny devices, smaller than grains of rice, could be used to restore health in a range of chronic diseases centered on organs and biological functions.

• These devices would be programmed to read and modify electrical signals that pass along nerves in the body, including irregular or altered impulses that occur in association with a broad range of diseases. The hope is that through these devices, disorders as diverse as inflammatory bowel disease, arthritis, asthma, hypertension and diabetes could be treated. We believe bioelectronic medicines could allow us to treat these with greater precision and fewer side effects than with conventional medicines.
Medtronic’s MiniMed 670G hybrid closed looped system, which is often referred to as an “artificial pancreas,” automatically administers or withholds insulin in response to blood glucose measurements, which it takes every five minutes.

It is the first FDA-approved device that is intended to automatically monitor glucose (sugar) and provide appropriate basal insulin doses in people 14 years of age and older with type 1 diabetes.

This system couples (1) a MiniMed insulin pump with (2) an Enlite® sensor that communicates externally using Medtronic’s Guardian® 2 Link system to (3) Medtronic Carelink® software which provides users easy-to-interpret trend reports and the ability to optimize therapy. This is all driven by a Bayer Contour® Next LiNK2.4 glucose sensor which wirelessly links to the MiniMed® 640G system.

Demand in the market this year for the MiniMed 670G system has been extraordinarily high, reflecting the potentially life-changing impact a closed loop system can have for Type I diabetes mellitus patients.
Example of Recent Innovation: “Dust” Implantable Sensors and Actuators

An ASIC chip (transistor) processes sensor measurements and creates signals which are to be transmitted out of the body.

Electrodes or related sensors can measure a wide variety of body states (e.g., nerve impulses, temperature, presence of cytokines).

This simple design involves less than 1 mm in cubic space and involves a fully functioning internal electrophysiological sensing and transmission system. Geometries as small as 50 microns possible.

Signals are received from the outside and transmitted back using ultrasound. No power is required here because ultrasound is converted to power using a piezocrystal (and vice-versa). A piezocrystal has the effect of converting mechanical stress into electric power.

Dust Sensors are Small
Radical Change in Medical Care Becomes Possible

The average American sees a doctor 1.6 times a year and is not heavily involved in managing their own care. It is not uncommon for severe chronic disease states such as diabetes to be poorly managed as a result.

We envision a world where consumers detect disease states sooner, treat disease states sooner and are much more involved in self-management of their disease states.

In a way, your body becomes more like a car that notifies you when an oil change is needed. You don't need to wait for your 50,000 mile checkup to figure this out.

“I am afraid you need an IL-1b antibody”

Implantable technologies have the potential to radically change routine medical care and positively impact hospital care.
Examples of Interesting Companies To Watch in Bioelectronics & Implantables Field

Mind Computer Interface
- facebook
- kernel
- Neuralink

Pharmaceutical Implantables
- Intarcia Therapeutics, Inc.
- Medtronic

Body Computer Interface / Bioelectronic Implantables
- CALA Health
- Galvani Bioelectronics
- Iota Biosciences
- Neuspera

Hospital and Implantables
- Baxter
- Boston Scientific
- Qualcomm

Disclosure: Torreya is an investor in Iota Biosciences.
7. Key Findings and Discussion

Summary
Key Findings

- We have used Torreya’s database of the pharmaceutical industry to size the pharmaceutical sector and have also used an econometric model to relate OECD estimates of future GDP growth to estimates of growth for the pharmaceutical sector.
- Despite widespread concerns about the slowing of innovation in pharmaceuticals, we predict that the pharmaceutical industry will grow substantially in the decades ahead.
- We estimate that the total revenue of the pharmaceutical industry will triple in real terms between 2017 and 2060.
- We have further noted that certain markets will see outsize growth. For example, we predict that the size of the China pharma sector will grow fourfold between now and 2060 while the European market will grow more slowly.
- The pharma industry is around 30% larger than previously thought and is one of top five in the global economy by total value (approximately $5.4 trillion today).
Near-Term Growth Will be Driven by Rare Disease Drugs and Biologics

- The rare disease sector is an important growth driver in the pharmaceutical industry. To illustrate, the pure play rare disease sector is now more than 17% of the value of the big pharma sector, larger than the entire biotech sector and larger than the entire Japan pharma sector or China pharma sector.

- Major innovations will continue to drive the size and growth of this sector with positive implications for the health of the global population.

- The pharmaceutical industry has historically been impacted by major changes in how drugs and medical devices are invented. In the 19th Century, pharmaceuticals were largely derived from natural substances.

- By the middle of the 20th Century pharmaceuticals were typically devised using chemical synthesis and by the 1980s innovations in drug design took hold as scientists learned to use structure-activity relationships to rationally design drugs.

- By the 1990s, the revolution in biologics had begun in earnest and today we are seeing the results from decoding the genome.
Key Findings and Discussion (Continued)

- In particular, the last decade has seen substantial accretion in industry valuations from adoption of biologics for the control of diabetes, inflammation and cancer.
- We expect to see continued growth in the biologics field, fueled by growth in new biologics such as Novartis’ Canakinumab (anti-IL1-beta monoclonal antibody) and by improvements in the manufacturability of peptides.

**Long-Term Growth Will be Driven by Nucleic Acids and Implantables**

- The long-standing effort to develop nucleic acids as therapeutics is starting to pay off. Longer-term, we expect substantial growth in nucleic acid drugs built through approaches that include microRNA, RNAi, direct mRNA, gene therapy and gene editing.
- The ability to regulate gene transcription and correct genetic mutations with therapeutic constructs has profound positive implications for human health and may ultimately reduce society’s reliance upon chronic therapies.
- There are a number of important areas of innovation that are likely to shape the future of the pharmaceutical sector including cell therapy and innovations in digital health.
Silicon Valley Likely to Make Its Presence Known in Pharmaceuticals

- We focus on the potential impact that Silicon Valley may have on the therapeutics sector. In particular, we are now starting to see the adoption of closed loop systems driven by technology for improved pharmaceutical delivery (Medtronic’s recent insulin delivery system is a good example).

- While other industries have been substantially disrupted by digital innovation (think the automotive sector), the pharmaceutical industry has not been substantially affected thus far. We believe that this could change in the next decade.

- We believe that very small implantables will be an important area for innovation in the future and note the recent investments made in this area by companies such as GSK, Google and Neuralink (Elon Musk).

- The low cost of silicon and the miniaturization made possible in implantables means that radical changes in the entire model of drug delivery will become possible in the not too distant future.

- We envision a future where medical monitoring and use of therapeutics is more continuous, more automated and more effective.
Successive Waves of Innovation in the Pharmaceutical Sector are Quickening

- It is interesting to note the quickening of the pace of innovation in the pharmaceutical sector. There are successive waves of drug approvals driven by innovation in how drugs are discovered, made and delivered.

- The chemical synthesis revolution took nearly a century to play out. In contrast, the first viable biologic therapeutics were produced by Genentech in the late 1970s. Today, the impact of biologics (antibodies and peptides) is being fully felt (a “revolution” about 35 years in the making). We will see further growth in biologics but would not be surprised if it takes 100-years for revenues from this drug modality to peak.

- Similarly, in the nucleic acids field we have gone from the first approval of an antisense drug by Isis in 1992 to multiple approvals today (25 years later).

- It is expected that many approvals will occur over the next several decades in the field of nucleic acid therapeutics.

- It also appears likely that the fields of cell therapy and regenerative medicine will see numerous approvals in the decades ahead.
The field of implantables and bioelectronics is very new and, yet, the first approval took place in 2016 (Medtronic’s artificial pancreas). We expect numerous additional approvals in the next decade in this area driven by the ease of applying the technology and speed in which silicon-based digital technologies can be adapted for therapeutic applications.

**On the Paradox of Cost Controls Amidst Rapid Industry Growth**

- It is paradoxical to observe the increasing use of pharmaceutical cost controls around the world at the same time that we are forecasting major market growth.
- Yet we have seen rapid pharma market expansion amidst cost controls. Market growth and pharmaceutical cost controls have gone together for decades.
- Quite simply, innovation in new products has outpaced society’s ability to pay for them, creating the need for cost containment.
- At the same time, access to pharmaceuticals has improved markedly. The poor and middle classes in many parts of the world have obtained widespread access to pharmaceuticals for the first time in the last two decades. The consequent increase in volume has been important in creating pressure for cost controls.
Overall, we see a Future with Tough Cost Controls and Continued High Long-Term Growth in the Pharmaceutical Industry

- Economic growth expands the social budget for pharmaceutical products but even more rapid innovation and access improvements driven by unmet medical need have created a need for cost containment policies.
- Because of the scale of the pipeline of new drugs to come in upcoming decades we expect cost containment policies, especially those aimed at older API’s, to continue and likely strengthen.
- A major benefit is that access will continue to improve worldwide. Today, much of the world’s population still cannot afford or obtain modern drugs.
- On the whole, the future is bright. Medical innovation accompanied by economic growth means that the decades ahead will see a much larger pharmaceutical sector.
- The pharmaceutical sector of the future will be very different than today’s market which is led by small molecule oral solid dose pills. The future sector will feature co-existence of chemical drugs, advanced biologics, nucleic acid therapeutics, cell therapies and implantables.
Thank You!
Appendix

About Torreya
Torreya: A Leading Global Investment Bank Serving Life Sciences Companies

Torreya is a global investment banking boutique serving companies in the life sciences industry. Since its inception in 2007, the firm has closed over $100 billion worth of deals across nearly 250 assignments spanning branded pharmaceutical, biotechnology, generic pharmaceutical, and life sciences companies. Our partners are senior industry bankers and executives, with deep experience, industry knowledge, and broad relationships. We are a partner of choice for companies seeking discreet, conflict-free and knowledgeable advice on M&A, capital markets, licensing and asset sale transactions.

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<th>Role Description</th>
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<th>Transaction Details</th>
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<tr>
<td>Acquisition of the generics business of Sawai</td>
<td>Upsher-Smith</td>
<td>Acquisition of phase III royalty interest</td>
<td>May 2017</td>
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<tr>
<td>Microbiome partnership with Allergan</td>
<td>Assembly Biosciences</td>
<td>$2.6 billion ($50 million upfront)</td>
<td>March 2017</td>
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<td>License of Gevokizumab to XOMA</td>
<td>Novartis</td>
<td>$438 million ($45 million upfront including debt relief)</td>
<td>August 2017</td>
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<td>Acquisition of the generics business of SELEXIS</td>
<td>$1.05 billion</td>
<td>$14 million</td>
<td>May 2017</td>
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<td>Sale of North American business to $203 million</td>
<td>Alphora</td>
<td>Sale to eurofins</td>
<td>June 2017</td>
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<tr>
<td>License of US rights to Sandoz</td>
<td>Durect</td>
<td>$293 million ($20 million upfront)</td>
<td>May 2017</td>
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<td>Sale of Intrathecal business to Piramal $203 million</td>
<td>Mallinckrodt Pharmaceuticals</td>
<td>Sale of biologics manufacturing services company to JSR Life Sciences</td>
<td>June 2017</td>
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<td>Sale of India women's health business to $35.9 million</td>
<td>Wafergen DMS</td>
<td>Has been acquired by Takara $35.9 million</td>
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<td>Sale of IP to CDMO to Eurofins</td>
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<td>Licensing of Gevokizumab to Sandoz DMS</td>
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<td>licensing of Gevokizumab to Sandoz DMS</td>
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<td>Sale of stake of US rights to Sandoz</td>
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<td>Licensing of Gevokizumab to Sandoz DMS</td>
<td>$1.05 billion</td>
<td>Joint Sell-Side Advisor $35 million on behalf of Accoand</td>
<td>May 2017</td>
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