Knall-Cohen Fund

Industry Report

US Large Cap Pharmaceuticals

December 15, 2018
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Initiation of Coverage

- **Initiation of Coverage**
  We have initiated coverage of the Healthcare sector, specifically companies in the pharmaceutical subsector. This subsector revolves around the market for consumer drugs such as biosimilars, novel/brands, generics, and therapeutics/specialty drugs. This subsector makes up 15.3 percent, of which 33 percent of that is pharmaceutical, of the S&P 500 as of December 13, 2018. Due to the non-cyclical nature of the demand for pharmaceutical drug products, the sector is characterized by low volatility and weak correlation to the overall market, which traditionally has been attractive for long-term investors and "buy-and-hold" strategies.

- **Pipeline Focus Ahead**
  Lately however, the rise of generic drugs and other brand-name alternatives has created downward pressure, away from traditional brand name drugs as consumers demand cheaper alternatives and many drugs experience a relatively recent loss of exclusivity. The investment scenario for the pharmaceutical industry as we know it is difficult in our opinion as many companies are experiencing all-time high valuations, and slowing pipeline development.

- **Companies of Interest**
  We have initiated coverage on Pfizer, Merck, Johnson & Johnson, AbbVie, Allergan, Bristol-Meyers Squibb, and Eli Lilly.
- **Forecasted Pipeline approvals coming in 2019**

Before discussing estimates of how many new drug applications (NDA) will be approved in fiscal year 2019, a brief mention of FDA’s history for approving drugs would be prudent. The FDA said on October 11th this year that it approved a record total of 781 generic drugs during its 2018 fiscal year, up from the previous record of 763 set last year. Part of the total number of approvals includes “tentative approvals”, or an ‘OK’ granted before patents on a branded drug expire, also increased from 174 in 2017 to 190 in 2018. The expansion of generic approvals is a part of the FDA’s goal of to resist high drug prices.

![FDA sets new record for Generic Drug Approvals](image)

As of 12/15/18, the FDA ‘s Center for Drug Evaluation and Research (CDER) approved a record number of new drug applications so far this year at 59, which could be potentially exceeded by the end of the year. Prior to this year’s expansion in approvals, the ten-year average was 32 novel drugs per year. Per year novel drug approvals look to outpace the yearly average over the near term as the FDA hopes to spur competition amongst pharmaceutical companies and increase affordability for patients.

![CDER’S Annual Novel Drug Approvals: 2008 - 2018](image)
**FDA Stages of Drug Development:**
When pharmaceutical companies look to add a new drug to their pipeline, the new drug could be one of several different types of drugs. It could be either a generic drug for an existing drug that lost exclusivity from its patent, a novel drug, or a biologic. Each new drug aims to provide a new treatment therapy that is better than existing treatments or is the first ever treatment for the problem. Depending on the type of treatment the pharmaceutical company wants to develop, the time from research and development to commercial use will vary significantly. A new drug alone will take an average of ten years, potentially longer, to complete the transition of initial discovery to commercial use. A generic conversely can take on average two years to develop before open access. Finally, biosimilars require approximately five to nine years of development and testing before commercial use. Below is a diagram of the process each type of drug will go through.

**New Drug Development Process**

*Discovery*

The initial stage of the development process begins with selecting a disease condition to target for treatment. Targeted disease conditions may be selected on the basis of new treatment technology, addressable market size, loss of exclusivity (LOE) on current pharmaceutical drugs, safety, tolerability, or convenience. Approximately 5,000 to 10,000 new molecules for any potential drug applicant are then tested to a thorough screening process including functional genomics and/or proteomics as well as other screening methods. Once a molecule has been found to interact with the disease condition target, scientist validate the target based on the level of activity between the molecule and disease condition versus effect of molecule on the target. Finally, after careful assessment, scientist chose the most promising molecules/compounds for further development.
Pharmacokinetics and Drug Disposition

Pharmacokinetics (PK) is the study of the time course of a drug within the body and incorporates the processes of absorption, distribution, metabolism, and excretion (ADME). Focus points in study are volume of distribution, the clearance of the drug, and the half-life of the molecules. These points help to answer the following questions: How large should the dosage be to get the desired effect? How fast does the body react to the drug? How often should a patient take the drug to feel its effects before they wear off? PK studies produce parameters such as AUC (area under the curve), Cmax (maximum concentration of the drug in blood stream), and Tmax (time at which Cmax is reached). Further into the development process, this data from animal PK studies is compared to data from early stage clinical trials to check the predictive power of animal models.

Preclinical Toxicology Testing and IND Application

Preclinical testing analyzes the bioactivity, safety, and efficacy of the formulated drug product. During the preclinical stage of the development process, plans for clinical trials and an Investigative New Drug (IND) application are prepared. Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials. During this time, FDA has an opportunity to review the IND for safety to assure that research subjects will not be subjected to unreasonable risk. Studies taking place during the preclinical stage should be designed to support the clinical studies that will follow. The following is a list of the primary stages of Toxicology testing.

- **Acute Studies:** this study observes the effects of one or more dosages administered to a test subject over a period of up to 24 hours. The goal is to determine toxic dose levels and observe clinical indications of toxicity. Usually, at least two mammalian species are tested. Data from acute toxicology studies helps determine doses for repeated dose studies in animals and Phase I studies in humans.

- **Repeated Dose Studies:** similar to the acute studies, repeated dose studies observe the effects of one or multiple dosages given to a subject over a longer period of time. This can be broken down to sub-chronic and chronic studies. The former lasts two weeks to three months in duration while the latter lasts six to nine months in duration.

- **Genetic Toxicity Studies:** The purpose of these studies is to determine the possibility of whether the molecular compound is mutagenic or carcinogenic (causes genes to mutate or develop
cancer). The pre-clinical studies are generally conducted to obtain the basic toxicological profile of new chemical entities (NCE). The toxicological data are used to evaluate the safety and efficacy of NCE, which will help in predicting the drug's likely risk/benefit assessment in New Drug Application (NDA) process.

- **Reproductive Toxicity Studies:** The general understanding of these studies is to determine any unfavorable effect on any aspect of male or female sexual structure or function, or on the conceptus or on lactation, which would interfere with the production of development of ordinary human beings. There are three Segments of the studies.

Segment one focuses on fertility and general reproductive performance. Tests involved in this segment typically use rats involving a standard treatment period of 60 to 80 days for the males and 14 days for female rats; each being given three dose levels.

Testing parameters used to validate the efficacy of the results can include the following:

- Fertility index = percentage of matings that result in pregnancy
- Gestation index = percentage of pregnancies resulting in litters of animals
- Viability index = percentage of animals surviving at least four days
- Lactation index = percentage of animals living at four days that survive the twenty-one-day lactation period

Segment two focuses on Embryo/Fetus Development (also referred to as Embryotoxicity studies). This test is usually conducted in two species: rats (*rodent*) and rabbits (*non-rodent*). The test involves three dosage levels and typically lasts 20 days for female rats and 30 days for female rabbits. Pups are delivered via a C-Section one day before expected parturition. Additionally, the uteruses are removed, weighed, and examined for dead or resorbed fetuses.
Testing parameters used to validate the efficacy of the results can include the following:

- **Fertility index** = percentage of mattings that result in pregnancy
- **Gestation index** = percentage of pregnancies resulting in litters of animals

**Females:**
- Weight gain and food consumption
- Number of implants and fetuses
- Post-implantation loss

**Fetuses:**
- Fetal and placenta weights
- External abnormalities
- Soft tissue abnormalities
- Skeletal abnormalities
- Death and retarded development

Segment three focuses on Perinatal and postnatal development. Tests involve rats, pregnant females, in groups of 20. Two to three dosages are administered from the end of organogenesis, the production and development of organs in the fetuses, through delivery and lactation.

Testing parameters used to validate the efficacy of the results will use any combination of parameters used in the prior segment tests.

- **Carcinogenic Studies:** The sole purpose of these studies is to determine largely if the drug will cause cancer. However, the studies are only necessary for drugs intended for chronic or recurring conditions.
- **Toxicokinetic Studies:** These are typically similar in design to earlier PK/ADME studies except that they use much higher dose levels. They examine the effects of toxic doses of the drug and help estimate the clinical margin of safety for patient use.

**Bioanalytical Testing**

The main emphasis of bioanalysis in the pharmaceutical industry is to obtain a quantitative measure of the drug or its metabolites for supporting the other studies of pharmacokinetics, toxicokinetic, bioequivalence and exposure-response like pharmacokinetic/pharmacodynamic studies performed in the later clinical trials. The testing entails meeting the requirements for reference standards and
standard curves, ensuring accurate quality control of studied molecule to meet FDA and European Medicines Agency (EMEA) acceptance criteria, and completing documentation requirements that exceed Clinical Laboratory Improvement Amendments (CLIA) standards. The testing requires separate lab spaces for clinical and bioanalytical testing to prevent illicit conduct or testing.

Clinical Trials
Broadly speaking, clinical trials test potential treatments in human volunteers, unlike the prior studies which involve rodents and non-rodents to see whether they should be approved for wider use in the general population. Clinical trials are designed to test a new potential drug in three phases.

- **Phase I**: studies assess the safety of the drug. This initial phase of testing, which can take several months to complete, usually includes a small number of healthy volunteers (20 to 100), who are generally paid for participating in the study. The study is designed to determine the effects of the drug on humans including how it is absorbed, metabolized, and excreted. This phase also investigates the side effects that occur as dosage levels are increased. According to the FDA, about 70% of experimental drugs pass this phase of testing.

- **Phase II**: studies test the efficacy of a drug. This second phase of testing can last from several months to two years and involves up to several hundred patients. Most phase II studies are randomized trials where one group of patients receives the experimental drug, while a second "control" group receives a standard treatment or placebo. Often these studies are "double blinded" which means that neither the patients nor the researchers know who has received the experimental drug. This allows investigators to provide the pharmaceutical company and the FDA with comparative information about the relative safety and effectiveness of the new drug. Also cited by the FDA, about one-third of experimental drugs successfully complete both Phase I and Phase II studies.

- **Phase III**: studies involve randomized and blind testing in several hundred to several thousand patients. This large-scale testing, which can last several years, provides the pharmaceutical company and the FDA with a more thorough understanding of the effectiveness of the drug, the benefits and the range of possible adverse reactions. The FDA approves 25% to 30% of drugs that enter Phase III studies testing.
Once Phase III is complete, a pharmaceutical company can request FDA approval for marketing the drug.

Generic Drug Development Process
Similar to the novel drug development process, the steps for bringing to market over a brand-name drug begin with generic drug application, an Abbreviated New Drug Application (ANDA), submitted to the FDA. Next, the generic drug needs to follow the outline requirements below:

Analytical Phase
- The generic drug is “pharmaceutically equivalent” to the brand. The generic drug needs to show that it is the same type of product (such as a tablet or an injectable) and uses the same time release technology.
- The manufacturer is capable of making the drug correctly.
- The manufacturer is capable of making the drug consistently. Generic drug manufacturers must explain how they intend to manufacture the drug and provide evidence that each step of the manufacturing process will produce the same result each time.
  FDA scientists review those procedures and FDA inspectors go to the generic drug manufacturer’s facility to verify that the manufacturer is capable of making the drug consistently and to check that the information the manufacturer has submitted to FDA is accurate.
- The “active ingredient” is the same as that of the brand. An active ingredient in a medicine is the component that makes it pharmaceutically active – effective at treating the illness or condition targeted.
- The right amount of the active ingredient gets to the place in the body where it has effect.
- The "inactive" ingredients of the drug are safe.
- The drug does not break down over time. Companies must do months-long "stability tests" to show that their versions last for a reasonable time.
- The container in which the drug will be shipped and sold is appropriate.
- The label is the same as the brand-name drug’s label. The drug information label for the generic drugs should be the same as the brand. drug’s label, so long as that removal does not take away information needed for safe use.
Bioequivalence Testing
The purpose studies are to ensure that the generic drug mimics the brand-name version in performance and efficacy. The bioequivalent studies are similar to the FDA clinical trials (Phase I, II, and III). Definitionally, bioequivalence is the absence of a significant difference in the rate and extent to which the active ingredient in a generic drug becomes present at the site of drug action when administered at the same dose under similar conditions in clinical studies of the brand-name drug. The “rate” and “extent” refer to the Cmax and AUC analyzed in novel PK and ADME studies.

Testing for drug will differ based on the product type (pill, liquid medication, nasal spray). Products are considered to be bioequivalent, if the 90% confidence interval of difference in the average values of logarithmic parameters to be assessed between test and reference products is within the acceptable range of log (0.80) - log (1.25). If AUC and Cmax are log-normally distributed, the bioequivalence acceptance range for each parameter is 0.80 to 1.25 when expressed as the ratio of the parameter’s population means for the test product and reference product. If AUC and Cmax are normally distributed, the acceptance range for each parameter is –0.20 to +0.20 when expressed as the ratio of the difference between the population mean for the test product and that for the reference product, to the population mean for the reference product. If the drug’s effect is not strong, a wider bioequivalence acceptance range than those above is sometimes set for Cmax. If Tmax is used as a parameter to evaluate equivalence, an appropriate bioequivalence acceptance range should be set beforehand.
**Biosimilar Drug Development Process**

A biosimilar drug is a biologic product that is approved based on demonstrating that it is highly similar to an FDA-approved biologic product, known as a reference product, and has no clinically meaningful differences in terms of safety and effectiveness from the reference product. As biosimilars are based on reference drugs, the drug development process is based on the novel drug development process with a few differences. Below the figure describes how.

The bio-originator manufacturer must produce an analytical package for the FDA that specifies the drug’s composition and formula. Preclinical testing must be undertaken to identify potential toxicities and, where relevant, demonstrate therapeutic effects in an animal model. *However*, the major work and costs for a bio-originator manufacturer relate to clinical trials. These range from phase I clinical pharmacology studies to clearly demonstrate the pharmacokinetics of the drug, through extensive phase II and III efficacy and safety trials to demonstrate unequivocal therapeutic benefit without excess toxicity.

For the biosimilar, in contrast, therapeutic benefit is already identified. Thus, most of the work for the biosimilar manufacturer relates to the analytical package, confirming that the product looks highly similar to the bio-originator in terms of its physicochemical characteristics as well as in terms of its composition, including impurities and aggregates, for example.
FDA Expedited Approaches to Drug Development

In order to accelerate the availability of medicines to patients with serious disease or where there is an unmet medical need, the FDA implements expedited approaches to accelerate the development and review of new medicines, such as:

**Fast Track:** expedites the review of drugs that treat serious conditions and fill an unmet medical need.

Benefits of the designation include more frequent meetings and communication with FDA to discuss the drug's development plan and ensure collection of appropriate data needed to support drug approval, eligibility for Accelerated Approval and Priority Review, if relevant criteria are met, and rolling review, which means that a drug company can submit completed sections of its Biologic License Application (BLA) or New Drug Application (NDA) for review by FDA, rather than waiting until every section of the NDA is completed before the entire application can be reviewed.

**Breakthrough Therapy:** expedites the development and review of drugs that may demonstrate substantial improvement over available therapy.

**Accelerated Approval:** accelerates approval for drugs that address a serious condition or fill an unmet medical need, based on a surrogate or an intermediate clinical endpoint.

**Priority Review:** accelerates FDA evaluation of drugs that, if approved, would be significant improvements in the safety or effectiveness of the treatment, diagnosis, or prevention of serious conditions.
Aging Population

The younger end of the “Baby Boomer” population class is to reach 55 years old in the coming few months. In terms of cyclical population growth, it seems we have just begun to hit the top-end of the aging population. With 17% of the United States Population over the age of 65 by 2020 and then 28% by 2060 according to the national census projections. The aging boomer population is here to stay. The healthcare story on this generation hasn’t changed much in the past three years but is still a key driver in today’s pharmaceutical space. Looking at the global development of this trend we notice that the United States is not even in the top 20 aging countries with 17% of the population over 65. Developed nations like Japan, Italy, Germany, and many more European nations’ average with elderly populations around 20%. This global aging population is a growing consumer base for pharmaceutical companies.
Research and Development is the core component of the pharmaceutical industry. According to Pharmaprojects, the average company allocates 17% of their budget to R&D. Although costs of R&D are likely to continue to increase as they have been for past 20 years, we calculate that the revenue gained from the development of successful treatment techniques in rare diseases to outweigh such costs. The cost burden of gene editing has come down significantly but is still more expensive than making a one size fits all pill. The cost is due to the complexity of new theory methods when attempting to treat rare diseases. Both gene and cell editing therapies fuel a variety of innovation for patients in spaces where traditional treatments are ineffective. Furthermore, Biosimilar Drugs and Biologics are creating competitive environment that fuels innovation and reduces development costs for new firms. A plurality of the focus in the R&D space has been toward cancer fighting treatments this proportion has grown from 27% to 34% in the past 8 years.
▪ **Mergers and Acquisitions**

2017 Tax reform has incentivized frequent buyouts of small cap biotech driving low level R&D in the Bio-Pharma space. The rise of inorganic growth in pharmaceutical industry is a trend that has been growing for the past 5 years and is likely to continue. Many companies will keep their eye on Nano-cap biotech firms and wait until their pipelines pass certain FDA trial mile markers and offer to buy out or enter into a licensing or partnership deal with the smaller company. These business strategies are done in an attempt to capture drug synergies between existing drug compounds and new treatment therapies. In reference to figure 5 from PharmaProjects, we see the trend of increasing active pipeline companies in the US despite high M&A activity in the sector. More and more unique companies with pipelines are popping up and are also being bought out at equally rising proportions. The race to find the cure to the most widespread and severe illnesses is ramping up. Large-Cap firms are using M&A to bolster their status as frontrunners in the race. On the other hand, a few companies like Pfizer are rearranging segments of their business in order to be prepared to divest irrelevant portions of their company, collect the tax benefits and reinvest the cash into an acquisition with more upside and higher synergy to existing projects. Most recently in January, Bristol-Myers Squibb (BMY) announced its plan to purchase drug maker Celgene (CELG) for a total of $74 billion.
- **Regulatory Reform**

According to Moody’s the repeal of the Affordable Care Act (ACA) would lower drug costs for branded drug companies. The ACA has been aided by pharmaceutical industry fees, rebates, and discounts. Elimination of these measures would benefit the sector as a whole if repealed properly. Unfortunately, the tangible affect would have little effect on companies that produce mostly generic drugs. This is because generics are not subjected to the ACA fees that brand names drugs are.

- **Medicare – The Overview:**

Medicare today provides benefits to 60 million adults and people with disabilities in a separate program called Medicaid. The number of Americans 65, the age at which one qualifies for Medicare coverage, and over will double, and the number of those 80 and over will nearly triple, between 2010 and 2050, according to a Kaiser Family Foundation report. Note that Medicaid coverage is not determined by age but rather by income and need. Despite the difficult intricacies in the American healthcare system, costs for care keep rising which will put pressure on the ability for Medicare (and Medicaid included) to meet demand among a growing number of qualifying consumers. Currently, it is estimated that 10% of the Medicare and Medicaid total budget is consumed by fraud and waste.

**Medicare Part B**

Part B covers 2 types of services

- **Medically necessary services:** “Services or supplies that are needed to diagnose or treat your medical condition and that meet accepted standards of medical practice.”
- **Preventive services:** “Health care to prevent illness (like the flu) or detect it at an early stage, when treatment is most likely to work best.”

**This includes:**

- Clinical research, Ambulance services, Durable medical equipment (DME), Mental health, Inpatient, Outpatient, Partial hospitalization, Getting a second opinion before surgery, Limited outpatient prescription drugs
- Overall Medicare Part B does not affect the pharmaceutical industry with the exception of certain drugs and products that are used in standard or common procedures.
Medicare patients pay a premium for this coverage and coverage is subject to change based on what plan consumers purchase.

**Medicare Part D:**

**Drug Coverage:**

Most Medicare drug plans have their own list of covered drugs, called a formulary. Plans cover both generic and brand-name prescription drugs. The formulary includes at least 2 drugs in the most commonly prescribed categories and classes. This helps make sure that people with different medical conditions can get the prescription drugs they need. All Medicare drug plans generally must cover at least 2 drugs per drug category, but plans can choose which specific drugs they cover. Most people who use Medicare utilize Part D as their main point of contact.

“For 2019 and beyond, plans meeting certain requirements also can immediately remove brand name drugs from their formularies and replace them with new generic drugs, or they can change the cost or coverage rules for brand name drugs when adding new generic drugs. If you’re taking these drugs, you’ll get information about the specific changes made afterwards.” – change to Medicare in 2019 that seeks to reduce drug cost by covering generic plans. This affects large companies as loss of exclusivity can severely reduce compensation for specific drugs as large consumer populations move away from the brand. This creates downward price pressure which is harmful for the industry overall.

To reduce cost structure, many plans place drugs into different tiers based on their cost and compounds; for which different plans group drugs into different tiers. Each tier costs a different amount. Generally, a drug in a lower tier will cost you less than a drug in a higher tier.
Description of the tiers:

**Tier 1**: lowest copayment: most generic prescription drugs  
**Tier 2**: medium copayment: preferred, brand-name prescription drugs  
**Tier 3**: higher copayment: non-preferred, brand-name prescription drugs  
**Specialty tier**: highest copayment: very high cost prescription drugs

For 2019, beneficiaries will have more Part D plan choices than in 2018, including 27 stand-alone prescription drug plans. A total of 901 prescription drug plans will be offered in the 34 plan regions in 2019 (plus another 11 prescription drug plans in US territories). This represents an increase of 15 percent in plan choice compared to 2018, and the second year in a row with an increase, following three years of plan reductions. For 2019, the average personal cost for a plan will increase 2 percent to $41.21 per month (estimate see figure below).

![Monthly Premiums for Medicare Part D with 2019 projected](image)

Based on figure 1 (see below) the cost estimates of prescription drug plans vary from $28 to $76 depending on the provider. Please note that roughly one million Medicare Part D enrollees who qualify as low-income individuals are estimated to receive roughly six premium free plans during 2019 that cost an average of $28 per month.
Part D consumers will experience higher cost-sharing amounts for generic drugs in 2019 but significantly higher prices for brand name drugs and non-preferred drugs, and a mix of copayments and coinsurance for different formulary tiers (see tier formulation above). Among the 10 largest PDPs, copayments range from $0 to $5 for preferred generics; $1 to $13 for generics; $25 to $47 for preferred brands; 32% to 50% coinsurance for non-preferred drugs (the maximum allowed for this tier); and 25% to 33% for specialty drugs.

*Non-preferred drugs are brand-name drugs that are not included on the plan's formulary (list of preferred prescription drugs). Non-preferred brand-name drugs have higher coinsurance than preferred brand-name drugs. You pay more if you use non-preferred drugs than if you opt for generics and preferred brand-name drugs. * - Express Scripts

**Medicare Advantage “Part C”:**

Medicare Advantage Plans, sometimes called “Part C” or “Medicare Advantage Plans,” are offered by private companies approved by Medicare. Medicare pays these companies to cover your Medicare
benefits. If you join a Medicare Advantage Plan, the plan will provide all of the consumer’s Medicare Part A (Hospital Insurance) and Medicare Part B (Medical Insurance) coverage. Although there are fewer Medicare Advantage plans offered, these plans were subject to wide discretion prior to the passage of the Affordable Care Act in 2010. Furthermore, 82% of Medicare Advantage plans come with a prescription drug plan which is optional under original Medicare. Currently, enrollment in Medicare Advantage stands at around 20 million. With options increasing for Medicare Advantage plan beneficiaries, premiums have seen sharp decreases. CMS reported “average Medicare Advantage premiums are expected to be the lowest they have been in three years, decreasing 6 percent from their 2018 level.” Almost half of all Medicare Advantage plan beneficiaries will pay $0 in monthly premiums during 2019, and 90 percent of plan beneficiaries will have access to Medicare Advantage prescription drug plans with no premiums. With a greater number of plans being offered both in Medicare Part D and Medicare Advantage, plan beneficiaries will see lower premiums across the board and increases in the number of drugs covered. Furthermore, increases in the number of plans could help consumers by allowing them to pick a prescription drug plan which meet their prescription drug needs. This could help to increase compensation rates for drug companies as the burden to compensate drug providers would fall on Medicare rather than the consumer. Further studies and changes into how Medicare compensate drug companies could also increase the percentage at which these drugs are compensated at, however this is a double-edged sword as although there are a greater number of fulfilled accounts receivable for specialty drugs, the dollar amount of fulfilled accounts receivable could drop for drugs which do not see significant consumer demand.
Distributed by state, the premiums paid by Medicare Part D enrollees in Florida, California and New York are the highest with the number of plans corresponding directly. Given population distribution, states with higher populations or a greater number of enrollees have the highest costs, but also the highest number of plans with New York has the highest costs, but a lower number of plans at 23, whereas California and Florida have 30 available plans and 27 respectfully. Having a variation in the number and cost structure of plans affects the pharmaceutical industry as service to different states has a disparate impact on the bottom line of companies seeking to promote the bottom line. Legally, the industry could face discrimination lawsuits over the future of their service as rural states have the lowest compensation structure.
In 2019, virtually all prescription drug plans will have a benefit design with all tiers for covered generic and brand-name drugs and cost sharing agreements in addition to the standard 25 percent base allowance. Expected in 2019, Part D enrollees will no longer experience a coverage gap when they go to receive their brand-name medications as more plans will allow consumers to choose what they need; which can help to increase compensation for Pharmaceutical companies and increase consumer access. Under changes in the Budget Act of 2018, Part D enrollees ‘out-of-pocket’ costs for brand-name drugs between the initial coverage limit and the coverage gap phase (point at which compensation for drugs stops) will decline from 35 percent of total costs in 2018 to 25 percent in 2019, a welcome change that was expected to happen in 2020, while costs distributed to patients for brands will decrease to 5 percent and manufacturer discounts will increase from 50 percent to 70 percent (also known as coupons commonly distributed for drugs).
Enrollees will pay an estimated 37 percent of the cost for generic drugs now covered under the previous coverage gap and plans (Medicare Part D) will pay 63 percent.

**Trends:**

**Pharmaceutical Companies Compensation to Doctors:**

In order to promote brand and non-preferred drugs to consumers, pharmaceutical companies spend billions of dollars each year to incentivize doctors to push their drugs. As plans vary by state as well as compensation for specific drugs, companies have different incentives in each state to promote their drugs as consumption in states with a higher number of plans offered can mean increased revenue from consumers both enrolled and not enrolled in Medicare Part D and Medicare Advantage. Specific reasons for how companies distribute incentive dollars could not be found, but a list below of the top ten states for drug prescription incentive funding towards doctors reveals a significant discrepancy towards compensation in California. We believe this to be the result of favorable funding and legislation on behalf of a liberal California government where enrollee premiums are among the highest in the nation. Going forward, we should expect that increases in patient premiums would have a direct, increasing effect on compensation for the pharmaceutical industry at large. Further breakdowns of top selling drugs (shown within this report) could reveal what drugs companies seek to push, aggregated against population distribution, could reveal a pattern in age, necessity, or profit margin as reasons for why certain states receive significantly more funding over others.
**Political Propositions to Medicare (and Medicaid):**

One fundamental change that’s favored by many conservatives in Congress is to convert Medicare into a voucher or “premium support” program according to outgoing House leader Paul Ryan. Today, Medicare pays the bills for most of a qualifying/enrolled consumer’s medical care. Under the proposed voucher system, each program beneficiary would get a flat amount of money each year to buy health coverage. If the care they need costs more than the voucher, the beneficiary would pay the difference. Others continue to promote raising the age of eligibility for Medicare to 67 or higher, leaving people in their 60s who do not have employer coverage to self-fund their health care.

The Trump administration has proposed expanding the availability of short-term, limited-benefit insurance policies for people who do not qualify or receive coverage through an employer or government program. But because insurers don’t have to cover individuals with preexisting conditions and can charge much higher premiums for older adults, experts say expansion of these plans could shut many 50 to 64 year-old consumers out of the insurance market.

According to a 2017 report from a meeting between AbbVie at Leerink Investment Bank, quote, “AbbVie believes that the intensity of the drug pricing debates and political risks is waning, and ... the company now sees little risk of significant changes in drug price regulation in the U.S., at least for the foreseeable future.” This quote can be placed in the context of top AbbVie executives, including chairman Richard Gonzalez, believing that despite political pressure from the Trump Administration, there is little appetite among elected officials to take serious actions against the pharmaceutical industry. We at team ten believe this is, in part, due to high costs of research and development that are involved in producing drugs. Having the ability to maintain price controls and exclusivity (patents) give drug companies major incentives to continue drug research which costs tens of billions of dollars on an annual basis in the United States alone. Team ten believes that the most likely course of action that congress, state governments or the private sector may take include: increasing state spending on Medicare and Medicaid programs, promoting generic drugs or changes to the structure of insurance as JP Morgan and Berkshire Hathaway, along with Amazon (in a separate imitative), are all trying to develop their own solutions that seek to optimize consumer cost with quality of care. Despite this, AbbVie management did note that their decision to cap price increases for drugs at no more than 10% citing recent political events. These likely references the
Mylan EpiPen scandal where makers of the common (brand name) drug chose to skyrocket the price following the anticipation of generic rivals. This caused massive uproar among public officials, consumers, and the media alike who all called for massive, industry-wide, price controls. While pharmaceutical companies are not currently concerned about price legislation, there is a fear that uncontrolled upward price manipulation could stoke public outcry and lead to a renewed effort among congressional officials to regulate drugs similarly to the European Union. The ethical issues around price gouging lifesaving drugs may cause unnecessary volatility in the company's stock which could be harmful to investors. Furthermore, decreases in federal budget spending on research and development grants creates a vacuum in which private (pharmaceutical) companies can maintain their hold on the process which disincentives price regulation the basis of need for innovation. Given recent changes in the political environment, the majority control of government could flip republicans to democrats. This might result in an increase in government funded research and research grants which could, in tandem, create pressure on congress to regulate drug prices.
**Five Forces Summary:**

Timeline: Before clinical trials can begin, a pre-clinical toxicity trial must take place to check the drug for toxicity in vitro (trial in a controlled environment without living organisms) and a virto toxicity trial must also occur using living organisms. These trials, along with all other clinical trials, are governed by the GLP standard that requires specific equipment, facilities, and personnel. Subsequent trials can take upwards of six years and require thousands of participants.

Chances of Approval: While success rates differ by phase and industry, on average there was a 9.6 percent chance of approval for all disease focused drugs between 2005 and 2015.
Distribution network: Large pharmaceutical companies utilize complex distribution networks and volume to create economies of scale by reducing logistical costs due to a steady stream of product outflow. Purchasing structure: Large pharmaceutical companies utilize relationships with pharmacy benefit managers (PBM’s) to drive sales volume and promote their drug lines. These relationships are developed over a long-term period and serve as a way to for established companies to monopolize the drug options available to consumers either through local pharmacies or doctors that work in connection with the pharmacy. Infrastructure: Given that the pharmaceutical industry manufactures many complex drugs while using machines worth tens of millions of dollars, the cost to open a single manufacturing plan can high extremely high as skilled labor must be brought in to handle most plant work. Due to high overhead costs, pharmaceutical companies are required to produce product batches in large volumes while smaller orders do not generate enough consistent revenue. Therefore, any pharmaceutical company must have substantial and continuous order volume to maintain operations. R & D: The main barrier to for new companies is the high cost of research and development. Last year Pfizer spent $7.657 billion on development of new drugs. According to Tufts University, the average cost of development for a drug stands at $2.6 billion, a 143 percent increase since 2003.
Buyer Power (expansion of Medicare Coverage):

Pharmaceutical manufacturers may sell drugs to health care providers, pharmacies and retailers, which then provide to the end users of the market. Some of the largest buyers in the US market include United Healthcare, CVS Corporation and Walgreens, all of which have strong financial muscle and purchase large quantities of drugs. Depending on the medical condition, there may be several different drug treatments available and product differentiation in these cases weakens buyer power. Such differentiation can include efficacy, ease of use, side effects, and cost-effectiveness. The move towards genetic and genomic research, giving rise to the possibility of personalized medicine, is also likely to decrease buyer power. Conversely, where generic equivalents to a branded drug exist, differentiation is decreased, and buyer power enhanced.

The primary source of funds for drug purchases in the US is public (e.g. Medicaid and Medicare) or private-sector health insurers. These may fund purchases directly, or they may reimburse some or all of an end-user’s initial purchase. This increases buyer power. Such large purchasers can exert monopsony market power.
**Supplier Power:**
A number of leading pharmaceutical companies have major investments in fine chemical manufacturing, providing them with a degree of self-sufficiency and this reduces supplier power to an extent. APIs are supplied on a contractual basis and so pharmaceutical companies are likely to risk high switching costs if they consider taking their business elsewhere. In turn, pharmaceutical companies employ sourcing managers to minimize costs and to mitigate supplier power. The development of new therapeutic agents requires the sourcing of newer APIs, for which chemical manufacturers can charge pharmaceutical companies’ higher prices. If the novel drug successfully reaches the market, the supplier of the API has increased buyer power and is able to make a large amount of money.

Market players tend to purchase their raw materials from numerous suppliers, reducing their reliance on any particular company. In general, laboratory equipment and chemicals show little differentiation between suppliers, with customers utilizing a high degree of choice in order to obtain the best quality and cost relationship, reducing supplier power. However, there are instances where specialized facilities or raw materials are required, such as sterile processing of biological materials. In such cases, supplier power is much stronger. It is unlikely that suppliers would forward-integrate into the pharmaceutical market; however, their capabilities in chemical synthesis make them ideal candidates for forward integration into the manufacture of generic drugs.

![Figure 7: Drivers of supplier power in the pharmaceuticals market in the United States, 2017](image)
Over recent years, larger pharmaceutical companies have turned to producing their own chemicals in a bid to enhance profits, however smaller companies lack the resources required to do this and remain reliant on API manufacturers. For instance, Teva has its own standalone business unit called TAPI (Teva Active Pharmaceutical Ingredients) which produces more than 370 APIs. Pharmaceutical companies will likely be keener to backwards integrate in APIs because those ingredients are essential to producing the final generic drug and are therefore going to be most in demand.
Threat of Substitution:
There are several substitutes for pharmaceuticals. Patients may choose traditional remedies. Physicians may opt for non-drug treatments if they consider them more appropriate. Successful drugs coming off patent also allow buyers to purchase generic drugs. Switching costs for patients here are relatively low. However, they may be more significant for the ultimate buyers, the healthcare providers. For example, suppose a national healthcare system reviewed the clinical evidence and decided that a chronic condition that had been treated by drugs taken for the patient’s lifetime could actually be treated by a simple surgical procedure. This would be a beneficial and cheap alternative. However, it might require more surgical teams to be trained and more operating theatres made available, which the healthcare system would also need to fund. These would constitute switching costs.

The main substitutes to branded drugs are generics and biosimilars (also known as follow-on biologics). Manufacturers of generics can offer the same drug at a much lower price, as they rely on the safety and efficacy data provided by the innovator product, and they therefore do not have to conduct costly clinical trials. Over the last ten years the U.S Food and Drug association believes generic drugs have saved $1.67tn. In 2017 the organization approved over 1,027 generic drugs for sale – another record and a figure which is expected to rise in the coming years. Recently revealed figures state over 89% of prescriptions in the United States are for generic drugs, an increase of 9% from 2016.
Use of complementary therapy in the United States continues to be popular, posing a substantial substitution threat which is enhanced by high health insurance costs. The National Center for Complementary and Alternative Medicine pushes the supposed benefits on the wider public. In 2010 the National Institute of Health allocated $520m for research in this area. Therapies for obesity will develop the market further, putting more pressure on conventional treatment. ‘Whole body vibration’ is being marketed as having the same benefits for treating obesity related illnesses as walking does. Public relations disasters for alternative medicine could lessen the substitution threat. The U.S. Food and Drug Administration (FDA) is currently reviewing the cases of eight babies who died after taking a popular homeopathic teething product, which was subsequently withdrawn from sale.
Degree of Rivalry:
The United States research-based pharmaceutical market is dominated by several multinational corporations, alongside smaller firms such as biotech players focused on a small number of new products; generics companies are also present. The presence of large international incumbents, as well as the number of companies operating within the market, increases the level of rivalry. The leading players in the US market include Johnson & Johnson, Pfizer, Merck and AstraZeneca. The US pharmaceuticals market is competitive as the concentration ratio of the four largest players amounts to 23.3%.

Compared to other countries in the region, the extent of consolidation in the market has been very large in the United States. One of the largest deals was worth $790m between Millennium Pharmaceuticals and Crescendo Biologics. The two companies have announced a global, strategic, multi-target collaboration and license agreement to develop Humabody cancer treatments. The size of the partnership and the potential profits which could arise from it show that rivalry in the United States has intensified.

A leading company in the United States, Pfizer, purchased the antibiotics arm of AstraZeneca for $1.5bn in 2016 among other purchases. This comes after efforts to buy AstraZeneca outright failed. Mergers and acquisitions have become the primary means of expanding market share in markets around the world, particularly for multi-national giants, demonstrating how intense rivalry has become. In June 2017, Johnson & Johnson completed its acquisition of Swiss biotech company Actelion Ltd for $30bn in cash after being approved by EU antitrust regulators. Large companies often lose revenue due to the expiration of patents and are increasingly motivated to acquire smaller companies that have a strong revenue potential due to innovative products.
Therefore, acquisitions are common in this particular market and are a key way for companies to establish a competitive edge. The practical benefit is reducing overall costs by increasing specialization, therefore eliminating research in less profitable areas. The down side is the possibility that drugs will be produced by fewer companies decreasing the chance of major breakthroughs. The goal of most startup pharma/bio tech companies is to sell out to larger companies.
- **Drivers**
  - Inefficient R&D operations fixed by merging technologies, AI, new strategic management ROI, and affordability Healthcare of healthcare across the globe.
  - Gene/cell editing therapies fuel new treatments where traditional treatments cannot be found.
  - Biosimilars & generics create a competitive environment that fuels innovation and reduces development costs for new firms.
  - The promise of M&A – frequent buyouts of small cap biotech companies drive low level R&D.

**Lowering Drug Prices Remains a Focus of Current Administration:**
The Centers for Medicare and Medicaid Services (CMS) released a proposal focused on reducing domestic drug prices and patient direct costs on November 26, with a key focus of the proposal being on providing Medicare Part D plans with increased flexibility to negotiate discounts for drugs in "protected" classes. For drugs in the six "protected" classes (antipsychotics, antidepressants, anti-convulsants, certain immunosuppressants and antineoplastic), the proposal would allow for the use of prior authorization and step therapy and allow for the exclusion of drugs that are simply new formulations of older single-source drugs or if the price of the drug increases beyond a certain threshold.

**Johnson & Johnson and Pfizer are most exposed:**
As shown again below in Figure 1, Johnson & Johnson (JNJ) and Pfizer (PFE) have the largest percentage of their NPV coming from drugs in protected classes, based on our proprietary PharmaValues database. Both companies have ~20-30% of their NPV coming from drugs in these classes. JNJ's exposure comes from its schizophrenia franchise and oral cancer drugs such as Imbruvica and Zytiga, while PFE's exposure is primarily through Ibrance and Xtandi. ABBV is also in a similar range, due to their partnership with JNJ on Imbruvica.
Not pictured in the chart (which focuses on larger cap companies) but also heavily exposed is ALKS, given Aristada and ALKS 3831, as well as royalties they receive from JNJ on other anti-psychotics.

**Additional Policies Focused on Medicare Part C and D Drug Spend:**
On protected classes, starting in 2020 the proposed policies include: 1) requiring Part D plans to tell enrollees and their doctors the patient’s out-of-pocket costs when a prescription is written; 2) allowing “step therapy” in Medicare Advantage (Part C) for Part B drugs, thereby encouraging access to high-value products such as biosimilars; and 3) prohibiting pharmacy gag clauses in Part D. As always, the details in the proposals, compared to what actually getting implemented, will determine the impact this will have on our companies, although the news further illustrates that the discussion around reforming US drug pricing will remain in the headlines and should remain in investors’ minds.

**Biologics & Biosimilars**

Biologics are predicted to comprise more than a quarter of the pharmaceutical market by 2020. Furthermore, the industry’s biggest biologics companies face revenue threats from biosimilars as well as the loss of exclusivity (LOE).

Lack of affordability and access to biologics is driving revenue growth for biosimilars, especially in emerging markets. In the European Union (EU), countries are seeing considerable cost savings with biosimilars, even when market share is low. According to Deloitte, biosimilars are around 30 percent less expensive.
The highest impact in US biosimilar sales is expected in the next two years, with an estimated 25 to 35 biosimilars expected to be on the US market by 2020. However, there is uncertainty about the regulatory environment for biosimilars which may hinder growth capabilities in the sector.

The Asia-Pacific region has more biosimilars in development than anywhere else in the world, led by China. China has the potential to become the frontier market for biosimilar drugs. The growth of biosimilars could push the industry into an innovative phase, even the potential for increased use of biologics.

**Orphan Drugs**

The orphan drug market is expected to almost double in the next five years, reaching US$209 billion in 2022. It's expected that these high-cost, specialized drugs have and will continue to face pricing scrutiny by policymakers. Of the top 100 drugs in the United States, the average cost per patient per year for an orphan drug was US$140,443 in 2016, compared to US$27,756 for a non-orphan.

According to the US Food & Drug Administration (F.D.A), 75 orphan drugs were approved in the United States in 2017, compared to a total of 27 in 2016 and 56 in 2015. The 50 highest-selling orphan drugs each averaged approximately US$637 million in sales. While only about 600 treatments are approved, 7,000 conditions are designated as rare in the United States. Major scientific advances will lead to even more rare diseases being identified and even more drugs seeking approval despite pricing pressures.

The passage of the new US tax law reduces the orphan-drug tax credits that biopharma companies can claim by effectively 40 percent. However, the reduction is not likely to change 'life sciences companies' strategies. The orphan drug market is a strategic market that solves unmet needs. The key benefits are not limited to a tax credit, but the other important aspects such as seven-year market exclusivity, faster FDA review and waived fees, and exception from the ACA branded drug pharma fee for orphan-only drugs.
**Therapeutics**

Oncology leads therapy areas in sales (Figure 4) and is likely to account for 17.5 percent of prescription drug and OTC sales by 2022, more than the next three highest therapy areas combined. In addition to oncology, the largest CAGR growth in the top 15 therapy categories will come from immunosuppressants, dermatologicals, and anti-coagulants.
Companies of Interest

Pfizer (PFE)

Pfizer Inc. engages in the discovery, development, and manufacture of healthcare products specializes in medicines, vaccine, and consumer healthcare. It operates through the Pfizer Innovative Health (IH) and Pfizer Essential Health (EH) segments. The IH segment focuses on the development and commercializing medicines and vaccines for internal medicine, oncology, inflammation and immunology, rate disease, and consumer healthcare. The EH segment is involved in development and supply of branded generics, generic sterile injectable products, biosimilars, and select branded products including anti-infectives.
Merck (MRK)

Merck & Co., Inc. engages in the provision of health solutions through its prescription medicines, vaccines, biologic therapies, animal health, and consumer care products. It operates through the following segments: Pharmaceutical, Animal Health, Healthcare Services, and Alliances. The Pharmaceutical segment includes human health pharmaceutical and vaccine products. The Animal Health segment discovers, develops, manufactures, and markets animal health products, such as vaccines, which it sells to veterinarians, distributors, and animal producers. The Healthcare Services segment offers services and solutions that focus on engagement, health analytics, and clinical services to improve the value of care delivered to patients.

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<th>Revenue (Million U.S. $)</th>
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<th>2Q</th>
<th>3Q</th>
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<th>Earnings Per Share (U.S. $)</th>
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<td>2015</td>
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<td>2014</td>
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Source: FactSet
Johnson & Johnson (JNJ)

Johnson & Johnson is a holding company, which engages in the research and development, manufacture and sale of products in the health care field. It operates through the following segments: Consumer, Pharmaceutical, and Medical Devices. The Consumer segment includes products used in the baby care, oral care, beauty, over-the-counter pharmaceutical, women’s health, and wound care markets. The Pharmaceutical segment focuses on therapeutic areas such as immunology, infectious diseases ad vaccines, neuroscience, oncology, cardiovascular and metabolism, and pulmonary hypertension. The Medical Devices segment offers products used in the orthopedic, surgery, cardiovascular, diabetes care, and eye health fields.

### Revenue/Earnings Data

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<tr>
<th>Year</th>
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<td>2015</td>
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<td>2014</td>
<td>1.54</td>
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<tr>
<td>2013</td>
<td>1.44</td>
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*Source: FactSet*
AbbVie (ABBV)

AbbVie, Inc. is a research-based biopharmaceutical company, which engages in the discovery, development, manufacture and sale of a line of proprietary pharmaceutical products. It is focused on treating conditions such as chronic autoimmune diseases in rheumatology, gastroenterology and dermatology; oncology, including blood cancers; virology, including hepatitis C and human immunodeficiency virus; neurological disorders, such as Parkinson’s disease; metabolic diseases, including thyroid disease and complications associated with cystic fibrosis; as well as other serious health conditions.
Bristol-Meyers Squibb (BMY)
Bristol-Myers Squibb Co. engages in the discovery, development, licensing, manufacture, marketing, distribution, and sale of biopharmaceutical products. It includes chemically-synthesized drugs or small molecules and products produced from biological processes called biologics.
Eli Lilly (LLY)
Eli Lilly & Co. engages in the discovery, development, manufacture and sale of pharmaceutical products. It operates through two segments: Human Pharmaceutical Products and Animal Health. The Human Pharmaceutical products segment includes the discovery, development, manufacturing, marketing and sales of human pharmaceutical products worldwide in the following therapeutic areas: neuroscience, endocrinology, oncology, cardiovascular and other. The Animal health segment operating through the Elanco Animal Health division, develops, manufactures, and markets products for both food and companion animals. The Animal health products include Rumensin, Tylan, Posilac, Paylean and other products for livestock and poultry, as well as Trifexis, Comfortis, and other products for companion animals.
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