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Abstract

The innovation in personalized therapies will continue to transform the healthcare industry. The 600 ongoing CAR T cell-therapy clinical trials, in the United States alone, is one example that illustrates personalized medicine will soon become a staple of the global healthcare industry. Most of the new gene and cell therapies are being targeted towards patients who have been diagnosed with a rare disease. Legislation and regulation have made Food and Drug Administration (FDA) approval more expedient for therapies targeting rare diseases – like the Orphan Drug Act of 1983. Such acts have made approval pathways quicker for these therapies, compared to therapies that are targeting the larger population. Naturally, sponsors of new personalized therapies have exploited such regulations to bring their therapies to market faster, while reducing the time and money it would take to go through the clinical trial process. Clinical trials for therapies that target rare diseases have lower requirements for the number of patients needed. Given the amount of innovation in biotech in recent years – including cell modeling that replicates human biology at very accurate rates – these lower requirements need to be reexamined to ensure that new therapies can be applied to as many patients as possible, and not only those who can afford it. The following papers discusses how this new wave of biopharmaceutical innovation came to be, and how new innovations in therapies should be guided by regulators to incentivize sponsors to include the most diverse set of patients possible when conducting clinical trials.

Keywords: Racial and ethnic disparities in healthcare, personalized therapies, biopharmaceutical innovation, rare disease treatment, orphan drug

Introduction

Currently, approximately 25 to 30 million people in the U.S. have been diagnosed with a rare disease. Although only ten percent of the population have been diagnosed with at least one rare condition, rare disease is an issue that affects all U.S citizens and the global health community. This is evident because the focus on innovation within the biopharmaceutical industry is shifting from aliments that affect a large amount of people to conditions that affect subpopulations of less than 200,000 citizens. The high costs of new drugs have been described in detail over the past four decades; the current uprising of new drugs is no exception. These high costs will create barriers – as they did in the past – for patients who cannot afford the expensive medications. However, there is an underlying issue with the wave of innovation for rare conditions. The number of patients available for the clinical trials of these new breakthrough therapies is much smaller than trials for more common conditions. Trials are not cheap as they require much effort from not only the manufacturers of the therapy, but also the hospitals, doctors and clinicians, and the patient. In most cases, the patient has to be insured, in a hospital that is participating in a trial, have a doctor recommend the trial, and have the time to be a part of the trial. These circumstances can severely limit the already small number of available trial patients, and clinical trials may only support subpopulations with certain socioeconomic backgrounds. This structure has the potential for leaving some U.S demographics out of the clinical trials, and it may also stop sponsors of drug medications to target subpopulations assumed suboptimal for clinical trials. Ultimately, this may force the biopharmaceutical innovation to apply to only certain demographics, and not to all. Thus, making innovation a major public policy issue. A healthier

population has lower health costs than one that is unhealthy. As this latest pandemic has shown, issues that affect the public tend to have harsher effects on vulnerable subpopulations.

Biopharmaceutical Innovation Is A Policy Issue

The wave on biopharmaceutical innovation – which includes personalized therapies, like gene and cell therapy – are focused on conditions that affect subpopulations that are insured, deemed suitable for clinical trials, and have the time and money to afford clinical trials. This can leave patients who do not fit these criteria with less innovative therapies. This is especially challenging for underrepresented subpopulations that have been diagnosed with a rare chronic condition because, not only are new therapies not being created, the existing ones have proved ineffective. This is an inhibiting obstacle for patient health; this is a setback for the global health community as a whole because of the lack of scientific research conducted on these subpopulations. Clinical research on these patients can lead to a broader understanding of rare diseases and increases the pace of innovation for all patients – including those that are underrepresented with rare conditions.

Measuring Innovation Within The Biopharmaceutical Industry

Quantifying innovation can be difficult. The main reason why it is difficult is the inability to quantify the spillover effects (and other intangible benefits). However, there have been several attempts to quantify innovation within the biopharmaceutical industry. Some attempts include counting the number of new therapies approved annually and measuring the internal rate of return (IRR) for research and development (R&D) expenses. The most common way of measuring

innovation within the biopharmaceutical industry is to count the number of FDA approved drugs within a certain time span, while being mindful of the time it takes to develop the drug. The amount of time it takes to bring a new therapy to market is lengthy, it can take three to fourteen years. There are three forms of therapies that the FDA recognizes, these are new molecular entities (NMEs), biologics, and medical devices. NMEs – according to the FDA – contain "an active ingredient that has never before been marketed in the United States in any form" This is basically any type of drug that is developed through chemical production – combining specific chemical ingredients to produce a drug. Biologics, however, are manufactured using mainly animal or plant cells. Biologics are considered to be more difficult to produce than NMEs. An FDA-approved medical device is – according to Section 201 (h) of the Food, Drug & Cosmetic Act, "an instrument, apparatus, implement, machine contrivance, implant, *in vitro* reagent, or other similar or related article, including a component part of accessory which is: recognized under in the official National Formulary, or the United States Pharmacopeia, or any supplement to them, intended for the use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man or other animals, or intended to affect the structure or any function of the body of man or animals. And does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. The term *device* does not include software functions excluded pursuant to section 520(o)." Biologics and FDA-approvable medical devices have received much attention over the past decade, while investments in both of these products continue to increase at a high rate.

An estimate for the time it takes to transition from R&D to the marketing of a new drug is eight to twelve years. Given this timeframe, there are many drugs that are in trial now and will be available within the next few years. Hence, any argument using the trend of the counting FDA-approved drugs to justify an innovation should be used with caution.

History Of Innovation Within The Biopharmaceutical Industry

Medical devices, and other biotech equipment, have always been a part of innovation. The Drinker Respirator (aka Iron Lung) was used to save a life of a pediatric polio patient in 1929, which set off an unprecedented amount of innovation within the biopharmaceutical industry. During the 1930s and 1940s, there were vast innovations in the process of drug discovery. Diseases that afflicted the U.S. population were beginning to be eradicated, such as polio and malaria. Complex (previously thought of as impossible) surgeries were being explored, and eventually mastered. This innovation occurs partly because of the legislation that fostered research and exploration; the innovation that took place during the 1930s and 1940s is largely due because of the organizational efforts of the federal government. Many of the therapies were still being understood, but the federal government enacted acts to quicken the pace of explorations and do it in an organized manner. For instance, in 1902, the Biologics Control Act is passed to ensure vaccines are safe for humans. The early 20th century also saw the FDA begin to take form; and, in 1938, the FDA formally has regulation authority over all prescription drugs, over the counter (OTC) medicines, therapeutic devices, and cosmetics. Thus, the FDA would begin shaping the landscape in which current biopharmaceutical firms operate. The arrival of the FDA's power not only gave shape to the market of healthcare in the U.S., it became a catalyst to create organizations that focused on health. The Communicable Disease Center (CDC) is established eight years after the FDA began regulating

therapeutic devices and cosmetics. Excitement throughout the medical community prompted research on a wide range of diseases. Both the federal government and the medical community saw their increasing expertise as a U.S.-controlled good that could be shared with other countries throughout the world. Shortly after the CDC began eradicating diseases in the U.S., they began to eradicate diseases in other countries. For example, after eradicating malaria from the U.S., the CDC set up malaria control programs in Southeast Asia in 1950. This illustrates, that innovation within the U.S. biopharmaceutical industry not only affects the health of U.S. citizens, but it can have influence on foreign policy.

Fast forward to the 1980s, after much focus on common ailments – such as asthma and diabetes – the FDA begins to concern itself with rarer diseases. The Orphan Drug Act, passed in 1983, created an official focus on diseases that affected less than 200,000 U.S. citizens. Unlike the common diseases, rarer diseases showed less promise of sales, compared to drugs that could be used by a wider target. In fact, during this time, most manufacturers of novel drugs for rare diseases were likely to incur a loss because their target of their breakthrough therapies may range from a person to 200,000 people. The Orphan Drug Act tries to address this problem by creating incentives for the development of therapies for rare diseases. The act offers both *push* and *pull* incentives to stimulate innovation for therapies that apply to a small section of the population. Some of the incentives included are seven years of market exclusivity, grants for clinical trials, and tax credits of fifty percent of the clinical trial costs. From the Act's inception (1983) to 1994, there were 96 approved orphan drugs. There were 164 orphan drugs approved from 1994 to 2005 – a seventy percent increase from the previous decade. An even larger increase would occur in the following decade, from 2005 to 2016, there were 298 orphan drug approvals – another seventy-seven percent

increases from the previous decade. Over the past five years (2016 – 2020), there have already been 293 orphan drug approvals. The main reason for the increases in novel therapies for rare conditions is largely due to the increase in innovation with biopharmaceuticals, especially regarding personalized medicine. However, there is an underlying reason why this number is starting to increase at a higher pace – legislation.

Clinical trials are notoriously known throughout the biopharmaceutical industry for being costly, both with time and money. The time it takes to complete a trial for a novel drug can last years. This is due to several factors. First, the first stage of clinical trials – phase 1 – is done to test the safety and efficacy of the new drug. For most trials (non-orphan), this is done with 20 to 100 healthy volunteers. This phase typically lasts several months, most of this time is due to administrative and logistical issues – as getting the volunteers may take some time. Seventy percent of trials make it past this stage. The second phase – phase 2 – takes longer than phase 1 because phase 2 trials are about efficacy and side effects. This requires a larger, yet more specific, set of patients. The second phase usually contains several hundred people that have been diagnosed with the targeted disease. This phase can last anywhere from several months to two years. Only thirty-three percent of trials makes it to phase 3 trials. Phase 3 trials is the final test before a drug is FDA approved. The first two phases have relatively lower levels of FDA regulation compared to the third. Phase 3 trials are done with 300 to 3,000 volunteers who have been diagnosed with the targeted disease. This phase is usually conducted over several locations with different hospitals. The stakeholders of a clinical trial include the FDA, the drug manufacturer and sponsor, the hospital, the doctors and clinicians, and the patient. Gathering these stakeholders for the common cause of testing the novel drug for efficacy and monitoring for adverse reactions can take years.

Phase 3 trials are by far the costliest of trials, mainly because of the number of patients involved. Only thirty percent of trials move on to phase 4 trials. Phase 4 trials (often referred to as after-market trials) monitor for adverse effects after FDA approval.

The decades of long, expensive, clinical trials caused so much strife for innovation within the biopharmaceutical industry. There have been innovations to address this issue – both regulatory and technological. Regulatory innovations with regard to trials have helped speed up the process for FDA approval. These regulations include – the fast-track and accelerated approval programs, the breakthrough-therapy designation, the Drug Development Tools Qualification program, the 21st Century Cures Act, and Orphan Drug Act among others. These FDA mandated programs allow for a faster approval for drugs that are deemed essential and, or, treat rare conditions. Innovation to address long trials are also coming from private resources. The shift on focusing on diseases that affect a smaller subpopulation calls for more specificity among trial patients. This has led Clinical Research Organizations (CROs) to create innovations, and adapt innovative technology from other industries, for clinical trial design. For example, CROs can use Artificial Intelligence (AI), and other machine-learning tools, to create more efficient clinical trials, compared to the old ways of gathering large groups of patients, and then later excluding some because they do not meet trial criteria. CROs can use their capabilities to select patients at a far more accurate level – compared to human selection, reducing (sometimes eliminating) the need to turn patients away because they do not meet the clinical trial's criteria. CROs target small biopharmaceutical firms who are either inexperienced with clinical trials or do not have the bandwidth to conduct them themselves. Traditionally, these smaller emerging biopharmaceutical companies would have to rely on the larger companies to conduct trials – usually requiring the smaller company to be

acquired by the larger. However, now given the capabilities of the CROs coupled with the FDA's commitment to a faster approval process, these smaller biotech and biopharmaceutical firms can target small populations without the help of large firms. For example, the FDA's Real Time Oncology Review (RTOR) – which allows for the FDA to review data on some oncology clinical trials in real time, enabling the FDA to provide suggestions and critiques in an immediate process instead of in a lagging submission and approval process – has been used with new technology-focused approaches to make clinical trials more efficient, in terms of time and money. Oncology trials, which has some of the longest clinical trials among all therapeutic areas, can be severely shortened because of these innovations. AI technologies combined with other biotech innovation – like cell models that replicate human biology *in vitro* – can lead to the elimination of phase 1 trials and reduce the overall trial time. In fact, Merck used an innovative clinical trial design, and received approval for their immunotherapeutic drug – Keytruda – in only four years after it began its phase 1 trial. Since Keytruda was approved, the novel drug can be approved to treat other ailments quickly, compared to a new drug that has been untested. Keytruda is now used for other indications, including Hodgkin Lymphoma.

Merck – one of the largest companies in the world, with 2018 revenue listed at $42 billion, is exploiting available tools to create therapies at a more efficient pace, compared to the decade (or more) it might take for most oncology therapies. Other large biopharmaceutical firms have, or will start to, use this method as the basis for most of its novel therapies because it saves so much time and money. Smaller and larger firms will target smaller populations to create novel therapies that target their diseases. The exploitation of new technologies and regulations enabled to speed up the approval process will lead to another increase biopharmaceutical innovation. In fact, innovation

has already begun to accelerate, CAR T-cell therapies – an extremely personalized oncology therapy – is the main focus for over 600 ongoing clinical trials in the U.S. Cell and gene therapy will be a large part of the next wave of biopharmaceutical innovation. However, this exploitation may come at the cost of other subpopulations, if regulation does not take steps to prevent imbalanced targeting. Smaller populations who receive a novel therapy may be a part of the same demographic or socioeconomic background, given the requirements for clinical trials. It is true that for therapies targeting diseases that affect less than 200,000 people in the U.S. require a lower number of patients for trials, compared to therapies targeting a larger portion of the population. This can cause clinical trials to ignore certain demographics and potential patients based on a few factors, ultimately clinical trials can be discouraged from taking patients that will harm the probability of trial success.

Conclusion

It is no secret that doctors are less likely to recommend clinical trials to patients who they suspect will jeopardize its success, even if the patient meets the criteria for the trial. Patient engagement is a crucial factor for the success of clinical trials. The awkwardness between racial and ethnic minority patients and white doctors has been documented and researched. An important implication of this relationship is the rate at which racial and ethnic minority patients are included in clinical trials – especially for oncology. Racial and ethnic minorities are not the only subpopulations that are subject to a lower likelihood of being selected for a trial; rural, uninsured, and lower-income subpopulations are some of the subpopulations who are less likely to be a clinical trial patient. However, all examples of subpopulations will have an underlying ethnic and racial disparity. Thus, addressing the racial and ethnic minorities issues with healthcare should be

assessed in each subpopulation researched. The jeopardy to an individual's personal health is clear, especially as therapies become more personalized. However, the disservice ethnic and racial disparities have on the scientific innovation of personalized medicine should be noted. A clinical trial that does not include the most diverse set of patients that fit the trial criteria, can be less insightful than a clinical trial that does. Public policy needs to address this issue, before the onslaught of new personal therapies become FDA approved. I recommend the FDA set up a subcommittee whose sole responsibility is ensuring the participation, innovation, and quality of health for racial and ethnic minorities.

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