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Biosimilars and Emerging Markets: Historical and Bioethical Considerations

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Introduction

There is not a more fundamental or personal topic than healthcare. In fact, the durability of this statement is proven across cultures, races, economies, and geopolitical boundaries. Healthcare captures the notion of well-being; a sense of being free from pain and the notion of normalcy in society. Irrespective of the methods and operational minutiae of global drug regulators, on a basic level, all share the common goal of ensuring that the healthcare needs of those they serve are being met. This goal is elusive, though, being often unfulfilled. Unfortunately, rather than being rooted in science and compassion, healthcare often becomes a function of economy and circumstance; leaving a trail of ethical principles in the wake of its shortcomings. A common denominator across all governments is the challenge of managing healthcare systems for maximum utility while controlling costs. Today, these governments are being given a new tool to maximize the effectiveness of their healthcare systems, the biosimilar. The seemingly simple concept of creating a cost-effective, similar complex recombinant antibody has become a topic for both scientific and public debate. The intent of this paper is to provide an overview of different forces shaping biosimilar policy in the traditional emerging market countries focusing on related bioethical issues.

The Regulatory Birth of Biosimilars

Any discussion of the ethics of the coming biosimilar wave would be incomplete if it were not properly framed by a brief summary of the stresses that have shaped the pharmaceutical landscape into what it is today. Biotechnologically derived therapeutic agents, so-called biologics, are a relatively new phenomenon in the drug world. While recombinant DNA technologies have been around since the 1970s, the development and commercialization of therapies derived from these technologies didn't really take off until the late 1990s and early 2000s, where a number of common monoclonal antibodies intended to treat a variety of ailments came to market. This was a phase shift for industry, which up until then was largely dominated by chemically derived small molecules. This shift occurred for a number or reasons, not the least of which was the implementation of the Hatch-Waxman amendment in the United States in the 1980's, which ushered in the era of generics [1].

Generics introduced competition into the pharmaceutical marketplace once their branded cousins went off patent. In the 30 years since Hatch-Waxman, the generics revolution forced companies to rethink their business models. As patents expired, innovator pharmaceutical companies undertook an innovation and technological renaissance which lead the development and commercialization of large molecule therapies called biologics. Biologics are not subject to Hatch-Waxman and, until recently, did not face the "patent cliff" challenges of chemically derived small molecules. With the will and technical innovations favoring large molecule development, companies continued investing heavily into the development and commercialization of these compounds. The traditional big pharmaceutical companies were joined by biotech startup companies which would catapult the innovative drug development business to new levels.

By 2017, biologics are expected to represent up to 20% of the global pharmaceutical market [2]. Further to this, in 2013, seven of the top ten selling drugs globally were biologics, with the top seller being Humira, which brought in over 11 billion dollars globally [3]. Clearly, biologics have supplanted traditional small molecules at the top of the pharmaceutical food chain, outpacing the growth of the industry as a whole [4]. However, a regulatory sea change is yet again putting its footprint on the world of drug development and commercialization. Biosimilars legislation in both the US and EU are again reshaping the development and commercialization environment in the pharmaceutical industry, with its impact only beginning to be felt.

The various biosimilar pathways offered by global regulators seeks to introduce a lower cost alternative to the biotherapeutics developed by originator pharmaceutical companies once their patent life expires. The legislative intent is to allow a fair patent life to originator companies to recuperate their development expenses while allowing the development of similar molecules to eventually introduce competition. Thus far, the focus of this paper has largely been on the United States and European Union due to their market size and the influence this has on the rest of world's pharmaceutical markets. However, biosimilars are having a much more global birth than the aforementioned generics. Namely, emerging markets are taking on a greater level of prominence in pharmaceutical business plans.

Emerging markets offer true growth areas in a world where developed markets face constant external pressures. Global pharmaceutical firms' involvement in emerging markets is growing exponentially. Nowhere is this more visible than in the arena of biosimilars. Emerging markets offer the alluring promise of willing clinical trial participants [5]. They are also attractive to industry because of the potential of the market expansion needed to fuel the growth the biotech industry desires. While the benefits of bringing research and eventual MAA filings to emerging markets does have a clearly visible upside, a number of considerations be explored.

The Rise of the Emerging Markets

The pharmaceutical industry has fully embraced globalization and is expanding into new geographies at a rapid pace. This is largely due to the fact that as the growth patterns in developed markets continue to flatten in the wake of patent cliffs and stagnant economies in the developed world. Priorities are shifting to high growth potential markets, the so-called emerging markets [6]. Globalization is forcing

multinational biotech companies to cut through traditional boundaries and push products to ever more remote corners of the world [7].

The significance of emerging markets isn't seen in the raw sales numbers. Emerging markets are still dwarfed by the revenue potential of the developed world. Their significance lies in their potential for growth. Emerging market economies GDP is growing at a rate that is far outpacing their developed counterparts, resulting in new middle classes while bring millions above the poverty line [8]. As these countries' economies continue to grow, there is an accompanying drive to modernize their healthcare infrastructures with a demand for chemical and biological therapies available from Western pharmaceutical companies. For instance, modernization efforts in China, Mexico, and Turkey have clear goals of providing health care coverage for all of their citizens by the end of the decade [9]. Emerging markets matter because 70% of the world's population resides there, accounting for a 31% share of global GDP. Further to this, by 2016 emerging markets will account for approximately 30% of global pharmaceutical spending [10]. It is because of this that biosimilars are a perfect fit for up and coming nations.

With millions of people and a tremendous unmet medical need, uptake of quality biosimilars is expected to be substantial. These markets, though, are not so easily reached by the Western multinational pharmaceutical companies. The heightened prominence of major emerging market countries has led to a series of steps being taken by their regulatory authorities with regard to foreign companies. Local favoritism or foreign infrastructure and manufacturing investments are becoming a common requirement in developing countries [11]. In short, local investment equals market access.

It should not be assumed, however, that all of the growth potential emerging markets offer or increasing affluence that their populations have achieved has led to bucolic societies. This is especially true in healthcare, where large disparities in access and allocation remain a persistent problem. Insufficient infrastructure and lack of consistent government programs leads to persistent healthcare disparities. The ethics of biosimilars is demonstrated as both public and private bodies attempt to address these issues. It is hoped that biosimilars, along with originator biologics, will be an important part of the healthcare equation in many emerging market countries by contributing to healthcare infrastructure development and public health maturation.

The Case for Biosimilars

If biosimilars are to live up to the expectations that have surrounded them since their inception in the early 2000s, they must do more than simply offer a marginal cost savings. In order for biosimilars to meet their true potential, they must be a key component in addressing global public health goals, and the emerging markets will be the proving ground for their utility. While the empowerment of emerging market regulators in pharmaceutical legislative policy and development is a positive aspect brought about by biosimilars, this relatively newfound prominence means nothing if it doesn't assist in fortifying the existing healthcare arsenal by uplifting the end user, which is the patient in need of a vital therapy.

The efficacy of biosimilar policies, regulations, and commercialization in the emerging markets as the basis for which we can say that biosimilars are, in fact, an ethical imperative necessary for protecting the basic tenets of autonomy, beneficence, nonmaleficence, and justice within the communities which they are researched and commercialized is a topic worthy of discussion. In more basic terms, do they protect the individual, do no harm, and promote good, all while promoting fair distribution?

A logical, as well as temporally relevant, starting point to begin the discussion on the ethics of biosimilars is at the research level. The sub-discipline of research ethics, as its name suggests, explores the nature of research and its impact of on the ethical well-being of subjects and the community as a whole [12]. Among the more tangible assets contributing to the conversation on research ethics is the Declaration of Helsinki. Born from the ethical abyss of World War II and picking up where the atrocities of Nuremburg were exposed, the Declaration of Helsinki and its periodic revisions are truly the ethical pillars which guide governments and industry, often via compulsory legislation, when conducting research on human subjects. Among the more notable and durable principles encased in this declaration is the sanction against conducting redundant research which offers the human subject little or no benefit [13]. An antagonists view states that the clinical research done to advance a biosimilar to commercialization, research that is mandated by governments to achieve marketing authorization, is a direct violation of the Declaration of Helsinki. Simply, it is argued that giving a research subject, generally a sick patient in need of treatment, a biosimilar is unethical since a known and proven treatment for the stated indication is already available via the innovator biologic molecule. On its face, this seems a rational argument. However, if this standard were to be applied universally, much of the clinical research that is done in drug and biologic development would be on the wrong side of this principle.

Clinical research studies often offer no physical benefit to research subjects. In the lifecycle of biotechnologically derived therapies, human bioequivalence testing is often done when a change is made to their formulas or compositions. These studies are done due to the human body's acute sensitivity to even the slightest change in their composition. The phenomenon called immunogenicity has been and always will be a major concern for biotechnologically derived therapeutics. Since no animal model is capable of predicting the human response to these medicines, even the most elementary changes to a formulation can cause a serious and unknown side effect [14]. As such, approved biologics are routinely vetted in humans when a formulation change occurs to ensure that the new formulation has preserved the overall efficacy and safety of the prior model. While this doesn't prove that it is ethical to test already available treatments in humans, it is the standard by which scientific evidence is gathered for their safe and effective use. To prove the ethical validity of these exercises, this type of testing must be seen as a means to increase the therapeutic options available to patients. When viewed through this prism, this research isn't redundant. Rather, it is a necessary step in the overall quest to increase wellness.

Based on the lack of wide market penetration of biotherapeutics in emerging markets, the research redundancy argument falls to the wayside. This is also the premise for considering the marketing approval of robustly developed biosimilars as ethically necessary since they, in conjunction with available originator biologics, help to ensure the universal medical imperative of treating those in need is being met. This is especially true in the developing world, where cultures and customs may value a more utilitarian approach to ethical judgment than the individualist approach commonly seen in the West. To guard against any sort of real or perceived ethical imperialism, one must approach situations with non-Western populations with ethical constructs based on public health and the so called "common good" [15].

This public health ethics approach, when used as a litmus test to gauge the ethical worth of biosimilar research and commercialization advances the conclusion that they are an ethical and essential component of emerging market healthcare infrastructure. Simply, biosimilars, whether under study or at the clinic, are a necessary component of the public health arsenal meant to increase the overall well-being of the population. The utilitarian principles of community betterment are upheld and advanced with the research and uptake of biosimilars into emerging market medical practices. Policy makers, developers, and medical practitioners can be assured that a robustly developed biosimilar offers the potential to supplement the toolkit of vital therapeutics. Caution, though, must be taken against the ethical interlopers seeking to reduce the quality and standards necessary to ensure patient safety and pharmacological efficacy. Intended copies present an ethical deviance with the potential to undermine the noble intentions of the biosimilar ideal.

Intended Copies and Public Health: A Lack of Standards

Intended copies are troublesome phenomena in developing countries. In the most basic sense, intended copies are biotechnologically derived drug products which lack the scientific rigor that goes into the development of an originator biologic or biosimilar. Most commonly, they lack true testing in humans as a condition of their marketing approval [16]. On its face, an intended copy would seem to be a welcomed component to the arsenal of accessible medications to combat diseases in populations with limited access to Western biotherapeutic innovation. This, however, is an ethical trojan horse. The promise of a cheap and readily available biotherapeutic copy should not come at the expense of compromising a drug's quality or a patient's safety. As stated earlier, the necessity of clinical testing for biologics and biosimilars lies in the nature of the molecules themselves. Biologically derived therapeutics offer great promise, but also offer great risk. Even the smallest environmental or physical changes to an established biologic or biosimilar can be met with harmful, even life-threatening, immunologic reactions. This is why the controlled development of biologics and biosimilars is essential to ensure quality, safety and efficacy.

Intended copies tend to not be assessed according to accepted regulatory standards and do not demonstrate similarity or sameness based on a rational, established development approach [17]. In fact, an intended copy can deviate significantly from the parent molecule it seeks to emulate, leading to any host of potentially harmful physical outcomes for the patient. It is because of this that an intended copy cannot and should not be considered an ethical way of providing access to patients in need of a biotechnological therapy. In a very succinct sense, the risk they pose does not outweigh the purported benefit they may or may not have. The very real possibility of doing harm, along with being mostly available only to impoverished populations should serve as a cautionary flag for any government, insurer, or patient that is being briefed on their potential "benefits". As stated earlier, biotechnologically derived therapeutics that have undergone a well-developed, robust development program should be considered for a patient's treatment options. It is ethically unjustifiable to accept anything less.

Discussion and Conclusion

Treating the individual meets the obligation of preserving the autonomy of a patient by recognizing that biosimilars increase access of needed biologic therapies to those individuals who have been historically and economically left behind. It is self-evident that a thoughtfully and robustly planned development program for a biosimilar ensures that the most good is achieved while potential harm is minimized, preserving the principles of beneficence and nonmaleficence. All of this ensures the tenets of a just system of healthcare allocation are met by allowing equal access to necessary, and now obtainable, life-preserving biotherapeutics in the form of biosimilars.

In short, emerging markets and biosimilars can be the model of a true collaboration between governments, research sponsors, the biotechnology industry, and the eventual patient. Ethically, it is imperative that we achieve this balance of safety, efficacy, innovation, and access.

Disclaimer

Dr. Leintz and Ms. Dedhia are currently regulatory strategists at Pfizer, Inc. The views contained in this paper do not necessarily reflect the views of Pfizer, Inc.

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