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Healthcare Professionals Knowledge and Attitudes Regarding Biosimilars in Northern Mississippi

Amanda Seals
University of Mississippi. Sally McDonnell Barksdale Honors College

Healthcare Professionals' Knowledge and Attitudes Regarding Biosimilars in Northern Mississippi

By:
Amanda Seals

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Approved by:

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Advisor: Dr. Anastasia Jenkins

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Reader: Dr. John Bentley

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Reader: Dr. Melissa Bass

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ABSTRACT

The emergence of biologics over the past the past few decades has led to a new interest in the production of a classification of drugs known as biosimilars. The vast complexity involved in the discovery, development, and manufacturing of biologics and biosimilars has made researching the knowledge and perceptions among healthcare professionals important.

Healthcare professionals must have an understanding of biologics, as these medications are used for some of the most rare diseases. Healthcare professionals in northern Mississippi were surveyed on their knowledge of and attitudes towards biologics and biosimilars in order to gain insight on the current status of the incorporation of these new therapies within the clinical healthcare setting. The knowledge questions included in the survey were input to assess the practitioners' knowledge of biosimilars' approval process, availability, and similarity to their reference product. The attitude statements were used to assess the practitioner's confidence and comfort levels in using these drug products.

Overall, the pharmacists correctly answered the highest proportion of the knowledge-based questions correct with 72.9% correct. Physicians followed with 61.5% correct and nurses with 60.2% correct. Overall, physicians were found to be most confident with the prescribing and the safety and efficacy of biologics. Physicians were also found to have high confidence in the pharmacists' involvement in the administration of biologics. All three groups of practitioners currently feel more confident with the

selection and administration of traditional drug treatments over biologics. However, each group of practitioners seems optimistic for a smooth transition of biologic therapy and the need for a standard protocol for doctors and pharmacists on the biosimilar substitution process.

These findings of this study are important in order to address the changes and improvements that need to be made regarding these wide range of products and their transition into the healthcare system. Further education regarding biologics and biosimilar medications must be provided to practitioners in order to ensure that all patients that may benefit from these medications have access to them.

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INTRODUCTION

Changes in the healthcare system of the United States occur every day in different ways. A recent addition to the healthcare system includes the introduction of biosimilars into the drug market. Biosimilars are a result of the advancement of medicines called biologics. Biologics are medications used to prevent, treat, diagnose, or cure a variety of serious and chronic illnesses including cancer, chronic kidney disease, autoimmune disorders, and infectious diseases (Biologics & Biosimilars).

A biosimilar is exactly what the name implies. It is a biologic that is "similar" to another biologic drug already approved by the U.S. Food and Drug Administration (FDA). Under U.S. law, a biosimilar is approved based on a showing that it is "highly similar" to an FDA-approved biological product, known as a reference product, and has no clinically meaningful differences in terms of safety and effectiveness from the reference product. Biosimilars are highly similar to the reference product that they were compared to in terms of safety, purity, and potency, but have allowable minor differences in clinically inactive components because they are made from living organisms (Biologics & Biosimilars).

The relatively new introduction of biologics has resulted in a gap in the knowledge about biosimilars among healthcare professionals. In 2014, the average age of female physicians was 47 years old and the average age of male physicians was 55 years old (Census). In May 2016, more than 26.2 percent of pharmacists were

55 years or older in age. The average age for pharmacists was 42.9 years of age (Department for Professional Employees). According to data from the 2008 National Sample Survey of Registered Nurses released in September 2010 by the federal Division of Nursing, the average age of the RN population is 47.0 years of age (AACN). Therefore, for each of these professions, the likelihood of biologics and biosimilars being included in their required professional schooling is unlikely. Ultimately, physicians, pharmacists, and nurses will influence the uptake and diffusion of biosimilars into clinical practice.

PURPOSE

Significance

Every healthcare professional plays a unique role in a patient's treatment of a certain disease. Therefore, the communication and understanding of different types of therapies among healthcare professionals is extremely important to ensure the best possible outcome for the patient. Advances in technology over the past few decades have led to major increases in the specificity and understanding of unique diseases and how to treat them. The emergence of biologics and biosimilars within the past few years has resulted in a lack of understanding of these medications because most professionals were not educated on them while in professional school.

Objectives:

The goal of this project is to determine how well these medications are currently being transitioned into our healthcare system, specifically in northern Mississippi.

The specific objectives for determining **knowledge** of healthcare professionals include:

1. Determining the basic level of understanding of a biologic product;
2. Determining the understanding of the origin of biologic products;
3. Determining the understanding of how biosimilar products are related to biological products regarding the indication, manufacturing process, and therapeutic outcome

The specific objectives for determining the **attitudes** of healthcare professionals include:

1. Determining their confidence in prescribing (or administering) biologics
2. Determining their comfort level of using biologics or biosimilars over traditional drug therapies
3. Determining their attitudes towards the future transitioning of biologics and biosimilars into our healthcare system and into clinical practice

BACKGROUND

Biologics are products manufactured using biotechnology and are made from living organisms (including humans, animals, and microbes) or synthetically. Biologics are usually made of larger, more complex molecules than traditional, small-molecule medications; and their structures are therefore more difficult to identify (Information for Consumers (Biosimilars)). The therapeutic target of a biologic is always a gene or a protein. Therefore, animal testing of biologics can be done to measure the drug's nature, chemistry, and effects and on its potential damage to the body. The fact that genetic information is decoded similarly among all cells, regardless of species, allows humans to study gene function in worms or zebra fish. Recombinant DNA, an important process for producing biologics, requires isolating the DNA from human cells and potentially modifying that DNA segment, inserting it into bacteria or a mammalian cell, and getting that organism or cell to express it. Several steps are involved in the development process: locating genes that code for proteins, cloning genes, reproducing the proteins associated with the genes, determining the role of the proteins in the disease process, and then developing a potential therapy (Morrow).

Biologics are not new; development of human growth hormone, insulin, and red-blood cell stimulating agents occurred decades ago, but the targets have increased exponentially with new genetic information and new understanding of subcellular cascades and disease processes. Scientific fields used in developing biologics include

genomics and proteomics, as well as microarray, cell culture, and monoclonal antibody technologies. Increasing knowledge of genetics and cell processes leads to potential new biologic (and drug) targets at each step in the protein-production process. This leads to new therapies, which in turn lead to a new understanding of diseases (Morrow).

Biologics have identified new targets for treating anemia, cystic fibrosis, growth deficiency, diabetes, hemophilia, hepatitis, genital warts, transplant rejection, and cancers. Biologics predict genetic propensity to diseases such as Parkinson's disease. Nondrug biologics include cultured tissues and immune system suppressants for transplantation and growth factors for tissue reconstitution to treat conditions such as diabetic foot ulcers. However, there is a greater potential for immune reactions to biologics than to chemical drugs. The molecules in chemical drugs are too small to be considered immunogenic and generally are not recognized by the immune system as "invaders." With biologics, depending on the drug, the human immune system can quickly identify the molecule and then mount an immune response to clear away a large molecule that it considers a foreign substance. This can destroy — or in rare cases, enhance — the activity of the biopharmaceutical (Morrow).

As with small-molecule drugs, research and development of biologics is expensive and risky, often ending in failure. While pharmaceutical companies target the most common diseases and conditions, biotech tends to target more difficult-to-treat populations that would be too small for pharmaceutical companies to be able to recoup drug-development costs. Yet, newer biologics also are targeting widespread diseases, with profound implications: a drug that costs $20,000 per year that is useful

for 1 person in 100,000 has much less effect on a health plan's cost structure than a $5,000-per-year drug that is useful for 1 in 100 people (Morrow).

Biologics have a complex production process that tends to yield small quantities. It is difficult to scale up biologics from laboratory quantities used for early analysis and preclinical testing to larger-scale batches and maintain product purity and batch-to-batch equivalence. Biologics are often extremely sensitive to physical conditions (temperature, shear forces, chemical phase, and light) and enzymatic action. They usually require complex bioassays for batch release and stability assessment, rather than chemical tests for identity and purity, which are required for small molecule agents (Morrow).

Biologics can cost thousands of dollars monthly and require special handling, as they are often less stable than chemically derived drugs and require controlled temperature and light, as well as protection from jostling when in liquid form. For example, many large proteins cannot be shaken to reconstitute, as shaking can destroy the protein structure. Biologics are medications targeted to specific genotypes or protein receptors. They are most commonly stored, handled, and delivered by specialty pharmacies and distributors that specialize in administering complex-molecule products for small populations. The distributors must have specialized handling and mailing processes in place to accommodate these complex medications. In many ways, biologics are considered designer drugs that are targeted for patients with uncommon diseases or for genetic subclasses of patients who have widely prevalent diseases. Biologic molecules are too large to be taken orally without being destroyed before passing through the intestine into the blood stream; therefore, they

usually are injected or infused. Also, potency is more difficult to quantify for biologic agents, and monitoring is a key component of early therapy. New modes of administration, such as via food that is directly or indirectly transgenic, are being studied. An example of the latter is goat's milk that produces an anti-malarial compound. Transdermally administered vaccines also are under investigation (Morrow). The elements involved in biologic therapy research and development have lead to the increasing importance of practitioners' knowledge of the availability and usefulness of biosimilars in order to reduce healthcare costs.

This reduction of healthcare costs of biosimilars is often compared to the cost reduction seen when generic medications began increasing in use following the enactment of the Drug Price Competition and Patent Term Restoration Act, commonly known as the Hatch-Waxman Act of 1984. This law encourages the manufacture of generic drugs. Hatch-Waxman established the abbreviated new drug application (ANDA) process that requires generic manufacturers to demonstrate that the generic is "bioequivalent" to an approved brand drug. Additionally, the generic manufacturer must file a certification regarding patents listed in the Orange Book (also known as Approved Drug Products with Therapeutic Equivalence Evaluations). This certification is a paragraph IV certification that states that the patent is invalid or will not be infringed and begins a process by which questions may be answered by the courts prior to expiration of the patent. Under Hatch-Waxman, FDA approval of an ANDA is automatically stayed for 30 months when a patent owner files a patent infringement lawsuit within 45 days of receiving a paragraph IV notification. During the stay, the FDA is prohibited from approving another ANDA. Additionally, the

first ANDA is granted a 180-day exclusivity period, as an incentive whereby the generic company does not have competition from other generic companies and can both establish market share and charge a higher price (Rumore).

Although the net effect of Hatch-Waxman on pharmaceutical innovation is ambiguous, its effect on generic drug development has been explicit, and the effect on consumers has been beneficial. Hatch-Waxman resulted in increased ANDA applications and paragraph IV challenges, especially since 1998. The effects of the Hatch-Waxman act are still being observed; 2016 was a record-setting year with more than 800 generic drug approvals (Uhl). There has also been a high success rate for patent invalidation, particularly formulation and polymorph patents. Since Hatch-Waxman, virtually all top-selling drugs not covered by patent face generic competition; whereas pre–Hatch-Waxman, only 35% had generics available. Similarly, today more than 70% of prescriptions are for generic medications, whereas pre–Hatch-Waxman generic prescriptions numbered 15%. At present, with rapid generic substitution, driven by tiered copays and formularies by third party payers, the rate of generic penetration is accelerated, with 80% conversion within 6 to 8 weeks. In addition to substantial generic penetration, generic prices are approximately 60% or less than brand (Rumore). Almost 80% of medication prescriptions written in 2011 were for generics, which saved consumers approximately $193 billion in that year alone (Miller). Under Hatch-Waxman, the average length of patent extension is 3 years. Overall, there have been some reduced returns on new drugs, but product life cycles have not changed significantly (Rumore).

Just as we see 'generic' versions of traditional, small-molecule medications enter the market following patent expiration of their brand-name product; a 'biosimilar' version of a biologic medication can be prescribed in place of the FDA-approved reference product (Information on Biosimilars). When Hatch-Waxman was conceived, the class of drugs called "biologicals" – which are derived from living cells and include vaccines, certain proteins and monoclonal antibodies – was inconsequential compared to small molecule drugs, but now they are both common and expensive, accounting for more than 15% of U.S. drug expenditures. Their worldwide sales are more than $150 billion annually, and growing rapidly (Miller).

Differences exist, however, between the small-molecule 'generics' and the large-molecule 'biosimilars.' Generic medications are exact replicas of their brand-name medications, and maintain bioequivalence (equivalent dosage form, safety, strength, administration route, quality, intended use, and pharmacokinetics) (Information on Biosimilars). With biologic products, the manufacturing process is part of the patent and is subject to regulatory approval. Process changes trigger the need for new clinical trials, yielding greater development costs. Partly to remedy this, the FDA's Center for Biologics Evaluation and Research (CBER) has developed draft guidelines for a post-approval comparability protocol allowing companies to combine several manufacturing changes into a single abbreviated post-approval application when they change their process. Companies are not required to duplicate clinical studies after a drug manufacturing change, if they can show that it is bioequivalent and causes no new adverse reactions (Morrow).

Biologics, though much more expensive than chemical entities, are generally considered by health care providers and payers to be worth their cost — as long as the appropriate patients receive them and achieve the desired clinical outcomes. Patients for whom biologics are a good value include those who have failed conventional therapies or for whom no other options exist. For some drugs, assays assist in patient selection. The cost of DNA-based tests and the expense of educating clinicians on their use must be factored into the net value (Morrow). This increase in the expenses of treatment has resulted in other companies producing biosimilars in efforts to produce higher profits. Biosimilar products, while highly similar to their biologic reference product, will structurally differ slightly from their reference product but do not differ in safety, purity and potency (Information on Biosimilars).

Interchangeable products are slightly different than biosimilar products, in that they must also be tested and tests must conclude that they produce the same clinical result as the reference product. The manufacturer must also prove that the safety and efficacy will not be reduced when switching to/from the reference agent if the medication is to be administered more than once. Lastly, in order to receive a biosimilar, the prescriber must write for the biosimilar specifically (write the name of the product on the prescription); however, a pharmacist without the intervention of the prescriber may substitute an interchangeable product (Information on Biosimilars).

Over the past two years, biosimilars have been approved via an abbreviated pathway that deems them 'biosimilar' or 'interchangeable' to their reference biologic product, based off of the original safety and efficacy studies upon which the original

biologic medicines received FDA approval. The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was originally sponsored and introduced on June 26, 2007. It was formally passed under the Patient Protection and Affordable Care Act and signed into law by President Barack Obama on March 23, 2010 (Information on Biosimilars).

Key differences between the Hatch-Waxman Act and the Biologics Price Competition and Innovation Act include a longer period of statutory exclusivity for biosimilars, no 30-month stay for a reference product sponsor upon initiation of litigation, and no 180-day market exclusivity period for the first filer of an application for approval of a biosimilar in the absence of interchangeability (Kowalchyk). The BPCIA recognizes the importance of encouraging innovation, but it also provides a pathway for competition once monopoly protection ends. Biologics can obtain patent protection, which lasts for 20 years from the date the patent application is filed. Questions exist about the degree of protection afforded by biologic patents. Accordingly, the BPCIA provides a 12-year market exclusivity and a 4-year data exclusivity beginning when the biologic drug receives FDA marketing approval. Each exclusivity can be extended 6 months for pediatric applications. A biosimilar cannot be marketed until the 12-year exclusivity expires. These exclusivity protections are intended to encourage biologic research and development. Patents can be challenged in court, but exclusivity cannot (Blackstone).

There is often a lag of many years between patent approval and FDA approval to market a drug; therefore, a patent may run out before the exclusivity expires. By contrast, it is important that the data exclusivity expire before the market exclusivity,

so that a biosimilar manufacturer can begin development work to ensure rapid market entry on the expiration of a biologic's market exclusivity. Furthermore, biosimilar entry would be encouraged by predictable approval requirements from the FDA and market acceptance, among other factors. This would decrease risk, leading to more entry and greater price discounting. The 12-year market exclusivity is a type of insurance policy, given the uncertainty of patent litigation, and is probably necessary to encourage innovation (Blackstone).

Biosimilars have a better chance of reaching the market as copying an available biologic is easier and less risky than creating a newly branded agent. In addition, the investment in biologics is much greater than in biosimilars, and the probability of success is lower. The best strategy for a biosimilar entrant may be to enter emerging markets, which have lower entry barriers, to develop strong post-marketing data to show that the product is truly a biosimilar, and then to enter more stringently regulated areas with an established record. The business of biosimilars has not developed as quickly as expected. Despite all the current difficulties, it is expected that the market will develop, given the potential profits with patent expiration. Moreover, the mandate to decrease healthcare costs and to increase access to these life-saving pharmaceuticals will increase the biosimilar market. Appropriate public policy should encourage biosimilars but should also ensure that they are safe. The biosimilar market will become more prominent, but this will take considerable time and effort (Blackstone).

As of September 2016, only four biosimilars had been granted approval from the FDA: Zarxio (biosimilar to Neupogen), Inflectra (biosimilar to Remicade), Erelzi

(biosimilar to Enbrel), and Amjevita (biosimilar to Humira). With a number of biological products soon to lose patent protection, more biosimilars are expected to enter the market. As with any new developments, there are likely to be some challenges, particularly since biosimilars, unlike generics, cannot be automatically substituted for branded products. While biosimilars mean savings for patients, pharmacists may need to facilitate the use of these products by engaging further with prescribers, insurance companies, and the FDA (Panesar).

For now, the high costs involved in planning, conducting and analyzing the results of clinical trials will prevent a stampede to make biosimilars. In fact, several major drug companies are pursuing the development of biosimilars as though they were completely new, independent and distinct products. Consequently, they have expressed their intention to submit a new Biologics License Application (BLA) to obtain marketing approval, rather than an abbreviated submission via the biosimilars pathway (Miller).

The bottom line is that for the time being, from a regulatory perspective each biosimilar version of an approved biological product will be regarded as, in effect, a completely new and distinct drug. Therefore, development costs will be higher and there will be far fewer biosimilars developed than generic versions of small molecule drugs. Thus, for the foreseeable future, savings to federal entitlement programs, insurers and patients will surely be much more modest than some of the hyperbolic predictions made by politicians and others (Miller).

Eventually, the availability of biosimilars will spur competition and reduce prices somewhat, and because of advances in technology, some of the follow-on

products may even be superior to the original brand-name biologicals. For now, the new regulatory pathway for most biosimilars will not be significantly abbreviated or greatly affect burgeoning health care costs (Miller).

The market for biologics and biosimilars will experience changes within the next few years. In addition, biosimilars will affect the healthcare system and the way in which healthcare professionals treat patients. There are several issues within the healthcare system regarding biosimilars that have yet to be addressed. A formal designation of interchangeability from the FDA will be another obstacle as drug makers, payers, doctors, pharmacists, and patients will contest a power struggle over whether a script can be transferred to the biosimilar and how. The current legislation for biosimilars regarding substitution and notification is varies widely. Some states may allow the pharmacist full discretion to make a substitution while others may require notifying the physician before or after a change. Until switching studies can show that a biosimilar does not raise the incidence of an immunogenic response, physicians will be expected to be extremely hostile to the idea of switching a patient who is being successfully treated by the innovator. Surveys conducted by Mark Ginestro, a principal at KPMG, demonstrated that physicians feel they will have a strong voice in the adoption of biosimilars (McDonald).

In addition to the physicians' opinions, it is important to take into consideration the understanding and opinions of biosimilars among other healthcare professionals. Recent assessments of clinician understanding regarding biosimilars suggest that messages about the safety, purity, and potency of biosimilars have the potential to influence perceptions substantially. For example, in a survey of 277

clinicians conducted by the National Comprehensive Cancer Network (NCCN) in 2011, over half of respondents, including physicians, nurses, and pharmacists, stated they were not at all familiar (36%) or only slightly familiar (19%) with recent developments pertaining to biosimilars. However, a recent Internet survey of 376 physicians yielded different results. The survey, reported in August 2012, was conducted for the Alliance for Safe Biologic Medicines, an organization whose membership includes Amgen, Genentech, and the Biotechnology Industry Organization and which advocates for the use of unique nonproprietary names for biosimilars and has expressed concerns regarding biosimilars interchangeability. In this survey, 24% of respondents stated that they were very familiar with or had a complete understanding of biosimilars, while 54% indicated some familiarity or a basic understanding. The survey also characterized the respondents' feelings toward biosimilars naming and interchangeability and the ability to maintain "dispense as written" authority for biosimilars. Based on these survey results, it appears that there are varying levels of perceived understanding of the biosimilars market. Both the manufacturers of the originator reference products and their biosimilars industry counterparts will be working to fill in the current educational gaps, an area where the branded-drug suppliers would appear to have the resource advantage (Lucio).

According to a recent survey, physicians are on board with biosimilar use, as long as the medications demonstrate safety and efficacy. In another survey of nearly half of U.S. physicians, it is anticipated that the expansion of the number of biosimilar prescriptions will occur in the next three years as biosimilar availability increases. Efficacy (89 percent) and safety (81 percent) outranked patient costs (71

percent) in determining whether healthcare professionals would prescribe biosimilars across all five specialties surveyed. Respondents ranked lower costs for patients as the main way that biosimilars could bring value to their patients. Practitioners also noted that the biosimilar's availability on the formulary system with which the physician was working was a key determinant in his/her ultimately prescribing the medication. Data was captured from board-certified physicians in specialties where biologics prescribing is significant, including dermatology, endocrinology, gastroenterology, oncology, and rheumatology. Oncologists were particularly ardent in their support, being the only specialty group surveyed that was likely to prescribe biosimilars to the majority of their treatment-naïve patients. Sixty-three percent of oncologists surveyed were likely to prescribe biosimilars to naïve patients, and 62 percent of oncologists would prescribe them to patients who had taken an original biologic and now were requiring retreatment (Hayes).

As drug information experts, pharmacists will have a critical role in leveling the playing field to support an accurate perspective on biosimilars within their institutions. Pharmacists will assist with evaluating product- and manufacturing-related parameters that are unique to biosimilars and their abbreviated regulatory pathway. Pharmacists will also need to review healthcare system and patient considerations, including economic considerations and issues surrounding use of biosimilars following transitions of care between the inpatient and outpatient setting (Griffith). Pharmacists play a key role in developing formularies used by physicians and hospitals. Therefore, pharmacists can also serve as key drivers to reducing out-of-pocket costs for patients and increase reimbursements while increasing biosimilar

use (Dotinga).

Nurses have a central role in the delivery of medicine and the education of patients; however, training for nurses on new products is often ad hoc and incomplete. As a result, nurses may be unaware of the complexities and consequences of using new therapeutic protein drugs such as biosimilars. With the advent of these medicinal products, nurses face new challenges in their role in patient care. Poor knowledge of biosimilar medications could result in serious medication errors, adverse events or a delay in desired therapeutic gain for the patient. Pharmaceutical education of healthcare providers is paramount to ensure patient safety as biosimilars are introduced into clinical practice (Salem).

There are key roles for physicians, pharmacists, and nurses in the advancement of biosimilars in the healthcare system in the United States. It is important that practitioners on all levels of the healthcare system have a clear understanding of biosimilars and their future. This will lead to a reduction in cost of some of the most targeted therapies for patients with rare diseases.

METHODS

Participants

A total of twenty-five surveys were collected from physicians, nurses, and pharmacists currently employed at Baptist Cancer Centers in Oxford, New Albany and Grenada, Mississippi. All three facilities are part of the Baptist Memorial HealthCare Corporation and are located in North Mississippi. Three physicians, sixteen nurses, and six pharmacists completed the twenty-five surveys.

Procedure

Surveys were distributed to the three oncology centers between March 1, 2017 and March 10, 2017 and health care professionals were asked to voluntarily complete the survey (see Appendix A). Survey questions were adapted from "Biosimilars: An Assessment of Current Clinical Knowledge and Attitudes" developed by Edward Li. This survey was previously used to identify knowledge and perceptions of oncologists regarding biosimilars and therefore fit the purpose of this research. No identifying data was collected on the surveys. The survey informed participants of the time it took to complete the survey, the absence of risk associated with the survey, and goal of the research being conducted. The survey begins with demographic information including profession selection (nurse, physician, or pharmacist), years of experience (practice), specialty (physicians only), and age. The purpose of the surveys was to gain insight about the knowledge and attitudes of healthcare professionals regarding biosimilars. Eight multiple-choice style questions were asked

to determine the practitioners' knowledge of biosimilars. Each knowledge question addresses a different area of biosimilars and their relationship to biologics. A brief amount of information was given to each participant following the knowledge questions in order to prime them for 6 statements regarding biologics and biosimilars. This information included defining biologics and biosimilars and the approval process for biosimilars in the United States and their specific indications. The statements were ranked using a Likert scale of 1-5 (1 being strongly disagree and 5 being strongly agree). Results were delivered to the principle investigators after completion and data was entered into MicroSoft Excel worksheet for storage and SPSS software for analysis.

Data Analysis

Survey results were analyzed using SPSS software package provided by the University of Mississippi. The knowledge questions of the survey were analyzed based on whether they were answered correctly or incorrectly. Unanswered questions or unidentifiable answers were marked as incorrect. Each question was individually analyzed for each profession and the average proportion of questions answered correctly was determined for each profession. The mean scores from the Likert scales were found for each statement from the attitudes portion of the survey for each profession. Exact p-values were determined using Fisher's exact test for the knowledge questions and the Kruskal Wallis test for the attitude statements. The Fisher's exact test was used due to the small sample size and to avoid relying on approximations and assumptions. The Kruskal Wallis test was used as it compares

two or more independent groups of different sample sizes and is a non-parametric test (does not make any assumptions from data).

RESULTS

Participant Demographics

Table 1 shows the demographic information of the healthcare professionals interviewed for this study. Of the practitioners available for surveying on dates that survey was administered, 100% (4/4 on March 1, 2017 in Grenada, MS; 7/7 on March 3, 2017 in Oxford, MS; 14/14 on March 7, 2017 in New Albany, MS) were completed. The professionals varied in years of experience and age. Figure 1 demonstrates that the majority of participants were nurses (16), followed by pharmacists (6), and physicians (3). As shown in Figure 2, the majority of participants had 10 or more years of experience, and those with 1 to 5 and 6 to 10 years of experience were identical. Figure 3 displays the age demographics of participants, with most participants' ages 35 to 54 years, followed by those ages 23 to 34 and 55 to 64 years of age.

Table 1: Healthcare Professionals Demographics Obtained from Survey

Participant	Profession	Years of Experience (Practice)	Age	Mean Composite Score for Knowledge-Based Questions % Correct
1	Physician	10+	55-64	50%
2	Pharmacist	10+	45-54	87.5%
3	Pharmacist	1-5	35-44	62.5%
4	Nurse	10+	35-44	50%
5	Nurse	1-5	35-44	87.5%
6	Nurse	10+	45-54	37.5%
7	Nurse	10+	35-44	37.5%
8	Nurse	10+	23-34	50%
9	Nurse	10+	23-34	12.5%
10	Nurse	6-10	35-44	25%
11	Nurse	10+	35-44	100%
12	Physician	1-5	35-44	37.5%
13	Pharmacist	1-5	35-44	87.5%
14	Pharmacist	10+	55-64	62.5%
15	Pharmacist	10+	45-54	50%
16	Nurse	6-10	45-54	100%
17	Nurse	10+	45-54	75%
18	Nurse	6-10	23-34	62.5%
19	Nurse	10+	45-54	100%
20	Nurse	6-10	23-34	100%
21	Nurse	10+	45-54	25%
22	Nurse	10+	45-54	25%
23	Pharmacist	10+	55-64	87.5%
24	Nurse	10+	45-54	50%
25*	Physician	10+	35-44	50%

*Participant 25 was the only physician to indicate his specialty as oncology.

Figure 1: Number of Each Profession Participating in Survey

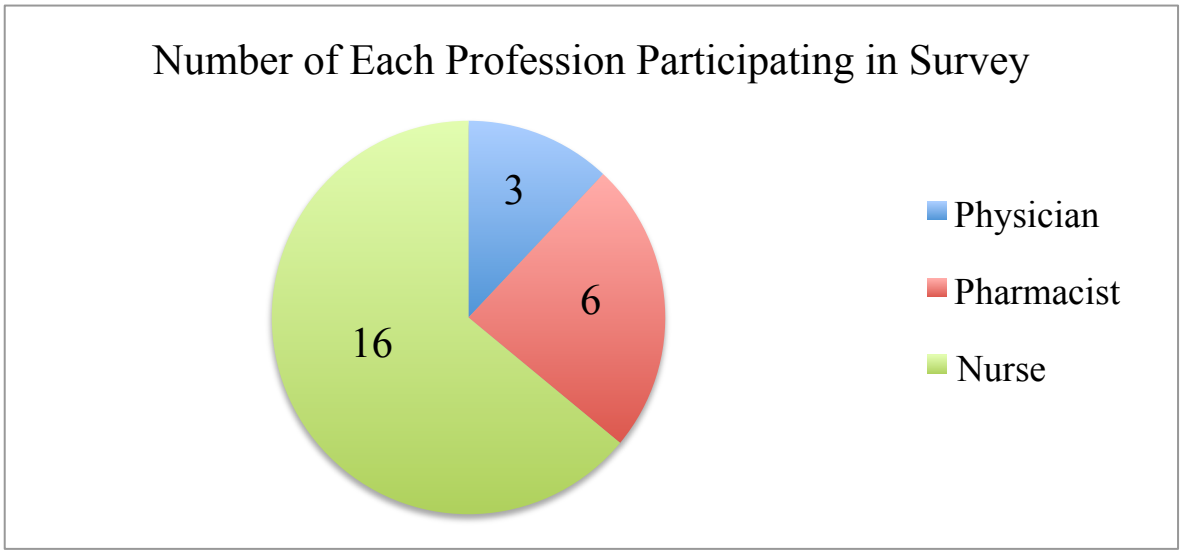


Figure 2: Years of Experience (Practice) of Participants

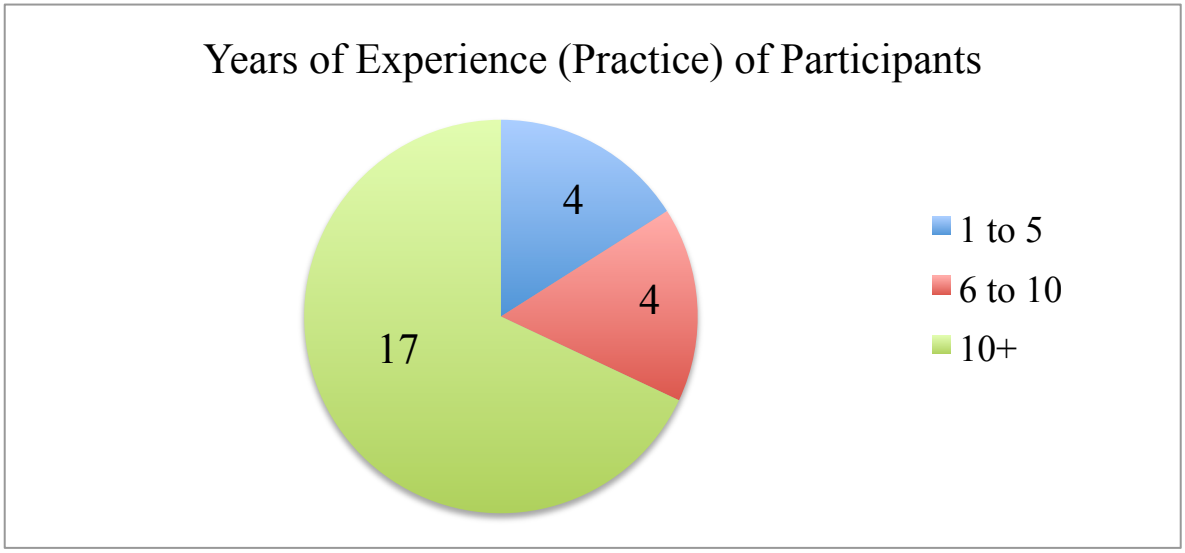
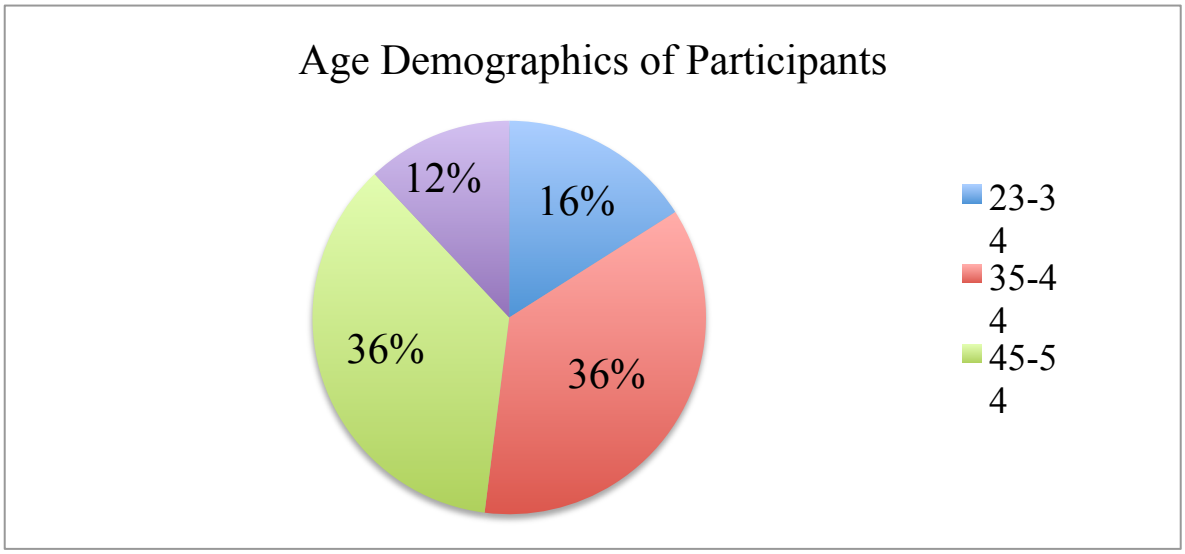


Figure 3: Age Demographics of Participants



Knowledge-Based Questions

Table 2 shows the percent of correct answers as a total of all of the professionals and of the professions broken down into physicians, nurses, and pharmacists. Each question varied in the percentage correct for each healthcare profession. Details of survey questions can be found in Appendix A. As shown in Figure 4, for knowledge question 1 (Survey Question 4), most practitioners answered the question correctly, with 66.7% of physicians and pharmacists and 56.3% of nurses providing the correct response. For knowledge question 2 (Survey Question 5), most practitioners answered the question correctly, with 81.3% of nurses and 66.7% of physicians and pharmacists providing the correct response. For knowledge question 3 (Survey Question 6), most practitioners answered correctly with 100% of pharmacists, 66.7% of physicians, and 56.3% of nurses providing the correct response. For knowledge question 4 (Survey Question 7), most practitioners

answered correctly with 100% of pharmacists, 75% of nurses, and 66.7% of physicians providing the correct response. For knowledge question 5 (Survey Question 8), most practitioners answered the question correctly, with 83.3% of pharmacists and 56.3% of nurses providing the correct response. However, no physicians correctly answered this question. For knowledge question 6 (Survey Question 9), most practitioners answered the question correctly, with 83.3% of pharmacists, 75% of nurses, and 66.7% of physicians providing the correct response. For knowledge question 7 (Survey Question 10), only 43.8% of nurses and 33.3% of pharmacists provided the correct response. No physicians correctly answered this question. For knowledge question 8 (Survey Question 11), 50% of pharmacists, 36.5% of nurses, and 33.3% of practitioners provided the correct response. Less than the majority of practitioners correctly answered knowledge questions 7 and 8 (Survey Questions 10 and 11).

Of the surveys received, 4 out of 25 were partially incomplete with some questions or statements unanswered. The pharmacists answered the highest proportion of questions correctly, followed by nurses and then physicians.

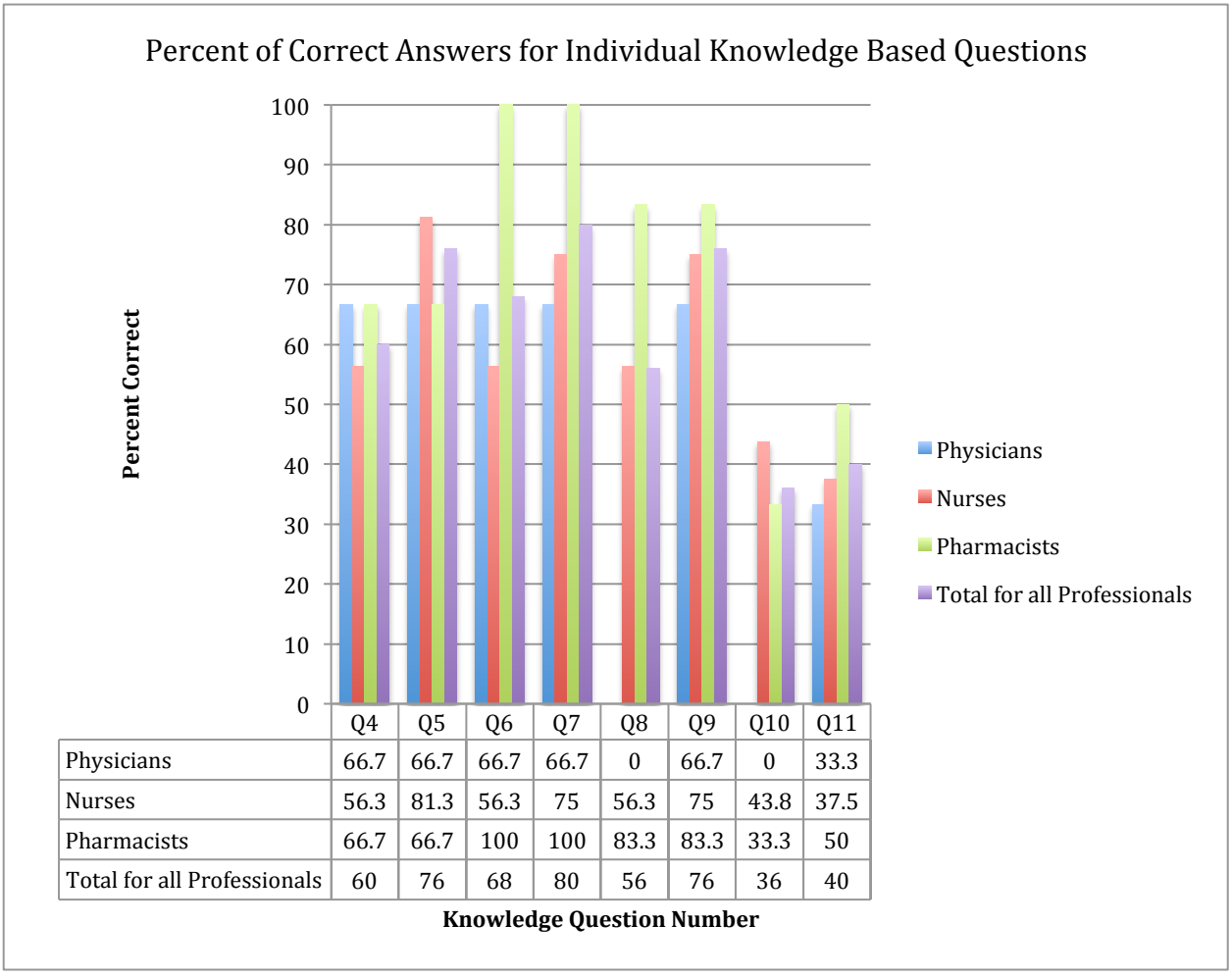
A mean composite score was calculated for each individual participant to identify the mean percentage correct for the knowledge questions.

Table 2: Percent of Correct Answers for Individual Knowledge Based Questions

	Total n=25	Physicians n=3	Nurses n=16	Pharmacists n=6	Exact P Value
Knowledge Question 1 (Q4)	60%	66.7%	56.3%	66.7%	>0.999
Knowledge Question 2 (Q5)	76%	66.7%	81.3%	66.7%	0.513
Knowledge Question 3 (Q6)	68%	66.7%	56.3%	100%	0.180
Knowledge Question 4 (Q7)	80%	66.7%	75%	100%	.447
Knowledge Question 5 (Q8)	56%	0%	56.3%	83.3%	.071
Knowledge Question 6 (Q9)	76%	66.7%	75%	83.3%	>0.999
Knowledge Question 7 (Q10)	36%	0%	43.8%	33.3%	.498
Knowledge Question 8 (Q11)	40%	33.3%	37.5%	50%	.843
Total Score	61.5%[1]	45.8%[1]	60.2%[1]	72.9%[1]	0.388

[1]Average Proportion Correct

Figure 4: Percent of Correct Answers for Individual Knowledge Based Questions



	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11
Physicians	66.7	66.7	66.7	66.7	0	66.7	0	33.3
Nurses	56.3	81.3	56.3	75	56.3	75	43.8	37.5
Pharmacists	66.7	66.7	100	100	83.3	83.3	33.3	50
Total for all Professionals	60	76	68	80	56	76	36	40

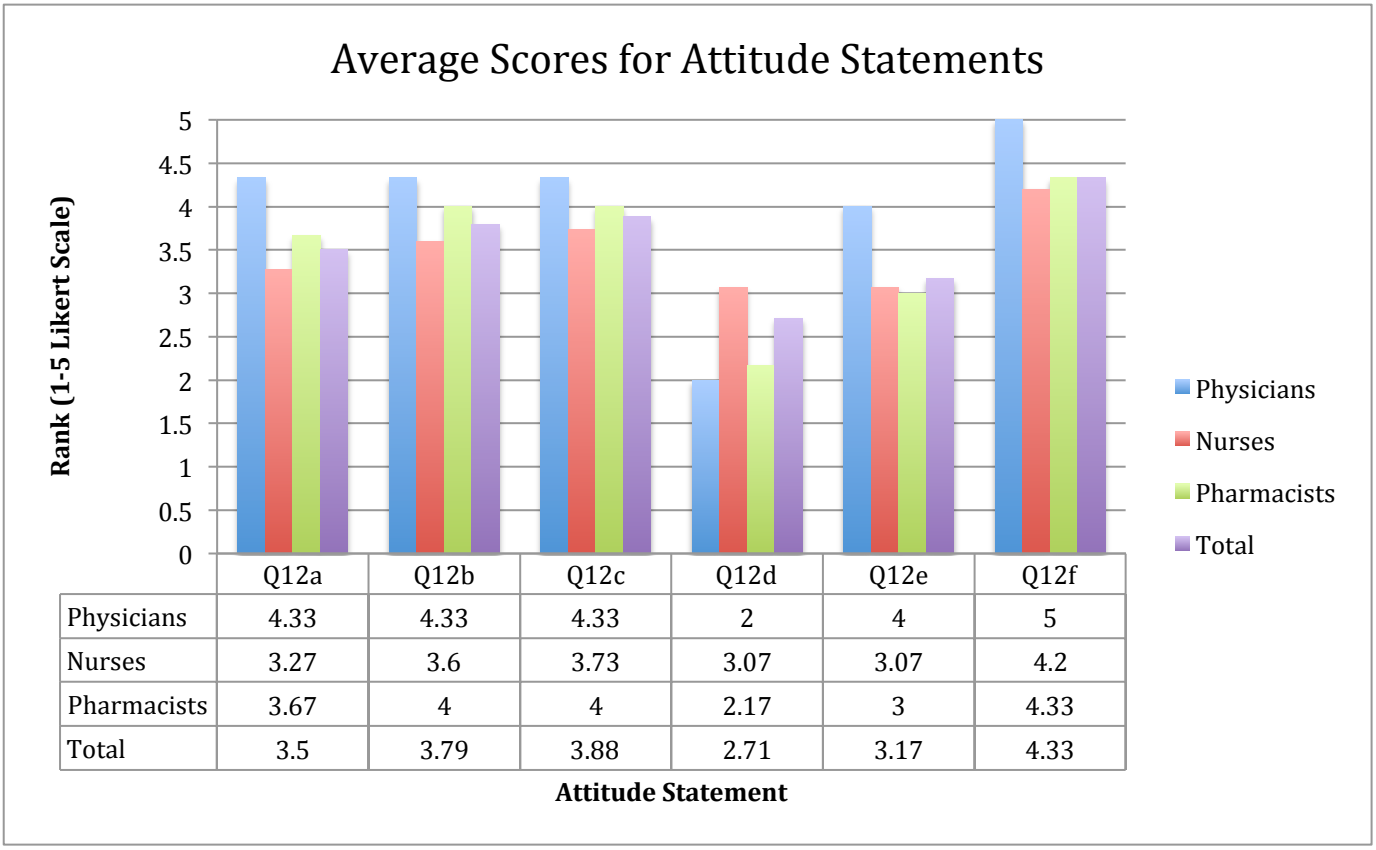
Statements Regarding Attitudes toward Biologics and Biosimilars

Table 3 contains the average scores for each attitude statement as a total of all participants (n=24, one participant failed to complete this portion of the survey) and the average score for each profession. Details of survey statements can be found in Appendix A. As displayed in Figure 5, for question 12a, which stated, "I feel confident about prescribing (or administering) the appropriate biologic drug for my patient population" physicians agreed and nurses and pharmacists were neutral. For question 12b, which stated, "If the FDA has approved a biosimilar, I would offer it to my patients because I am confident it is safe and efficacious" physicians and pharmacists agreed and nurses were neutral. For question 12c which stated, "I feel confident that the pharmacist will make the appropriate drug selection if an interchangeable drug is used without this information being communicated to me" physicians and pharmacists agreed and nurses were neutral. For question 12d which stated, "I am more likely to select (or administer) a traditional drug to treat one of my patient's conditions than an interchangeable biologic product because I do not believe they are therapeutically equivalent" physicians and nurses disagreed while nurses were neutral. For question 12e, which stated, "I do not perceive any barriers in appropriate selection of biologic drugs as pertains to my clinical practice" physicians agreed while nurses and pharmacists were neutral. For question 12f, which stated, "I believe we need a standard guideline for both doctors and pharmacists on the biosimilar substitution process" physicians strongly agreed and nurses and pharmacists also agreed. All statements excluding Statement 4 were more strongly agreed upon than disagreed among the total population of healthcare professionals.

Table 3: Average Scores for Attitude Statements

	Total n=24	Physicians n=3	Nurses n=15	Pharmacists n=6	Exact P Value
Statement 1 (Q12a)	3.5	4.33	3.27	3.67	0.099
Statement 2 (Q12b)	3.79	4.33	3.60	4.00	0.294
Statement 3 (Q12c)	3.88	4.33	3.73	4.00	0.627
Statement 4 (Q12d)	2.71	2.00	3.07	2.17	0.183
Statement 5 (Q12e)	3.17	4.00	3.07	3.00	0.367
Statement 6 (Q12f)	4.33	5.00	4.20	4.33	0.324

Figure 5: Average Scores for Attitude Statements



	Q12a	Q12b	Q12c	Q12d	Q12e	Q12f
Physicians	4.33	4.33	4.33	2	4	5
Nurses	3.27	3.6	3.73	3.07	3.07	4.2
Pharmacists	3.67	4	4	2.17	3	4.33
Total	3.5	3.79	3.88	2.71	3.17	4.33

DISCUSSION

Knowledge-Based Questions

This survey indicates several areas in which additional education about biologics, biosimilars, FDA approval processes, interchangeables, and reference products are necessary.

Physicians and pharmacists (66.7% answered Q4 correct) had a better understanding of how biologics differ from traditional small-molecule drugs than nurses (56.3% answered Q4 correct). Overall, 60% of the practitioners answered this question correct. This indicates that further education regarding biologics needs to be initiated.

Question 5 addresses the production of biologics. Overall, 76% of the practitioners correctly answered this question, indicating that most are aware of how they are produced differently from small-molecule drugs.

Question 6 addresses what the FDA requirements for manufacturers show in order to be classified as a biosimilar. Overall, 68% of practitioners correctly answered this question. However, 100% of the pharmacists surveyed correctly answered this question. This indicated the need for the education of physicians and nurses from pharmacists. Pharmacists are considered drug-experts and it is important for them to help physicians understand the relationship of biosimilars to biologics in order to increase the proper prescribing.

Question 7 addresses how interchangeable biologics are related to generic small molecules. A similar pattern is observed with this question as with Question 6. Overall, 80% of the practitioners answered this question correctly, with 100% of the pharmacists answering it correctly. This demonstrates the need for pharmacists to facilitate the education of physicians and nurses on the relationship between interchangeables and generic small molecules and their ability to be substituted at the pharmacy.

Question 8 addresses the FDA definition of a biosimilar and its relationship to its reference product. Overall, 56% of the practitioners correctly answered this question. None of the physicians accurately answered this question. This demonstrates a potential lack of knowledge regarding the clinical meaningful differences between the biological product and the reference product in terms of safety, purity, or potency of the product.

Question 9 had a stronger correct response of 76% of the practitioners. This indicates that most understand that biosimilars have the same (but not necessarily all) approved indications for use as the reference product.

Question 10 had an extremely low amount of correct answers with only 36% of the practitioners answering correctly. This question addresses that the FDA considers human pharmacokinetics and pharmacodynamics studies fundamental for demonstrating biosimilarity. It is important for the practitioners to have a better understanding of the background of biosimilars in order to be able to confidently prescribe and administer them to patients.

Question 11 addresses the differences between substitution and interchange of a drug. Overall, 40% of the practitioners correctly answered this question. These general definitions of substitution and interchange are vital to the understanding of biosimilars. The general lack of knowledge about switching, interchangeability, and overall safety of biologics and biosimilars cannot be ignored, as these factors are likely to inhibit uptake of them into the healthcare system.

The average proportion of questions answered correctly by all practitioners surveyed was 61.5%. This is not an acceptable score but can most likely be contributed to the relatively new market of biosimilars and their introduction into the healthcare system. With four biosimilars approved by the FDA and more than 60 in development, this survey highlights the need for greater biosimilars education for physicians and healthcare professionals. A continuing education course offered to the practitioners could help improve the understanding of biologics and biosimilars.

The mean composite score shows that each practitioner was highly variable in his or her individual knowledge.

Statements Regarding Attitudes toward Biologics and Biosimilars

Statements 12a, 12b, and 12c all address the level of confidence the practitioners have toward biologics, biosimilars, and interchangeable products. Physicians were most confident about these statements. This indicates that there is an important gap that needs to be filled regarding the physicians' knowledge of the biological products and their confidence in prescribing in order to help patients

understand their therapy. Confidence needs to be higher for these statements for each healthcare profession.

Low agreement levels (2.71) were found for Statement 12d among all practitioners. This statement indicated that the practitioners do not necessarily want to choose traditional drugs to treat patients when a biologic product is available. This is a positive finding for the incorporation of biologics and biosimilars within the healthcare system.

Statement 12e had a medium level of agreement (3.17) among the total of practitioners. This indicates that the practitioners are uncertain about the carriers that may affect the appropriate selection of biologic drugs.

Statement 12f had a high level of agreement (4.33) among the total of practitioners. This indicates that the practitioners believe there needs to be a standard guideline for both doctors and pharmacists on the biosimilar substitution process. This is an important step in the right direction for the diffusion of these treatments within the healthcare system.

The overall confidence regarding biosimilars can be increased with education regarding the new concepts of the approval and relationship to biologics. The high acceptance levels show that the incorporation of biosimilars into the healthcare system will be strong within the upcoming years as more biosimilars are approved. It is important for the practitioners to have a better understanding of biosimilars in order to improve the treatment of patients.

Limitations

The data resulting from the twenty-five surveys may not represent the general population of nurses, physicians, and pharmacists due to the small sample size collected. The low survey count is due to the geographical limitations of the study and the smaller size of the oncology centers surveyed. Furthermore, respondents varied in their knowledge of biosimilars. Therefore, the applicability of some of the more complex questions is uncertain. Data from this survey indicate that more education regarding the principles surrounding biosimilars is necessary. The knowledge of recent biosimilar developments was suboptimal among respondents. Despite the relative unfamiliarity, much interest in using biosimilars was still observed. The need for additional education is probably due to of the novelty of this concept in the United States. Provider interest, and therefore the need for additional education, will likely increase as more biosimilars are approved and enter the market.

APPENDIX

Appendix A

Survey Guide:

You are invited to take part in the following research survey about biosimilars. The research is being conducted by Anastasia Jenkins (BMH-NM Pharmacist) and Amanda Seals (pharmacy student). Your participation will require approximately 5 minutes. There are no known risks or discomforts associated with this survey. It is our hope that you will learn a bit more about biologics and biosimilars while taking this survey. Taking part in this study is completely voluntary. If you choose to be in the study you can withdraw at any time. Your responses will be kept strictly confidential, and digital data will be stored in secure computer files after it is entered. If you have questions or want a copy or summary of this study's results, you can contact me at alseals@go.olemiss.edu. Completing this survey indicates that you are 18 years of age or older and indicates your consent to participate in the research.

Q1: Please select your profession: Nursing / Physician / Pharmacist

Q2: Please circle your years of experience (years of practice) as a nurse/physician/pharmacist: 1-5 6-10 10+

Q1a: Physicians only: Please indicate your specialty (if applicable):

_____

Q3: Please circle your age: 23-34 35-44 45-54 55-64 65+

The following questions discuss biologics and biosimilars. Please select the most appropriate answer for each question:

Q4: Select an aspect of biologics that differentiates them from traditional small-molecule drugs.

a. Biologics require a lengthier FDA approval process.
b. Biologics are structurally large and complex molecules.
c. Biologics are less likely to cause an immunogenic response.
d. Biologics are made using a relatively simple manufacturing technique.

Q5: Which of the following is true regarding biologic products?

a. A biological molecule can be completely characterized using modern-day techniques.
b. Biologics are not sensitive to external conditions.
c. Biologics are made from living organisms and therefore contain an intrinsic level of heterogeneity within the final pharmaceutical product.
d. The manufacturing process typically involves simple chemical reactions and can be replicated by other companies with ease.

Q6: The FDA requires a manufacturer to show that a biosimilar:

a. Is interchangeable with the reference product
b. Has a lower immunogenicity than the reference product
c. Is therapeutically equivalent to a generic counterpart
d. Is highly similar to the reference product with no clinically meaningful differences

Q7: Interchangeable biologics are similar to generic small molecules in what regard?

a. They are generally appropriate to be substituted for the branded counterpart at the pharmacy
b. They are generally less efficacious than their branded counterpart
c. They are generally less safe than their branded counterpart
d. The quality of the products is generally inferior to the branded counterpart

Q8: The FDA defines a biosimilar as a biological product that is highly similar to a US licensed reference biological product except for minor differences in inactive components that there are:

a. No clinically meaningful differences between the biological product and the reference product in terms of safety, purity, or potency of the product
b. Minor clinically meaningful differences in product purity but no clinically meaningful difference in safety or potency between the biologically product and the reference product
c. Minor clinically meaningful differences in potency of the product but no clinically meaningful difference in safety or product purity between the biological product and the reference product
d. No clinically meaningful differences in safety between the biological product and the reference product but the purity and potency of the product can have minor clinically meaningful differences

Q9: If the FDA clears a product as a biosimilar, which of the following is true regarding the reference product?

a. The biosimilar will have different indications for use
b. The biosimilar will have the same (but not necessarily all) approved indications for use as the reference product
c. The biosimilar will be required to have the same packaging as the reference product
d. The biosimilar may have a different safety profile to the reference product

Q10: According to the FDA guidance on biosimilars, which of the following is "fundamental" for demonstrating biosimilarity?

a. Studies evaluating structure and function
b. Human pharmacokinetics and pharmacodynamics studies
c. Clinical safety and efficacy
d. Postmarketing studies, including phamacovigilance

Q11: Select one of the criteria that differentiates between "substitution" of a drug and "interchange of a drug:

a. Substitution means that the pharmacist selects and dispenses a drug product identical to the branded product in terms of active ingredient, strength, concentration and dosage form but with a different administration route.
b. Therapeutic interchange occurs when the pharmacist selects and dispenses a drug product that is not identical to the branded product's active ingredient but exhibits similar pharmacologic and therapeutic responses

c. Substitution occurs when the pharmacist selects and dispenses a medication that is not identical to the active ingredient, but exhibits similar pharmacologic and therapeutic responses

d. Therapeutic interchange occurs when the pharmacist selects and dispenses a medication that is identical to the active ingredient and exhibits similar pharmacological and therapeutic responses

Please read the following information concerning biosimilars and rate your opinion on the questions that follow. Please do not return to previous questions after completing this final section of this survey.

- Biologics include a wide range of products such as vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues and recombinant therapeutic proteins. Biologics can be composed of sugars, proteins, or nucleic acids or complex combinations of these substances, or may be living entities such as cells and tissues.
- In contrast to most drugs that are chemically synthesized and their structure is known, most biologics are complex mixtures that are not easily identified or characterized.
- A biosimilar product is a biological product that is approved based on a showing that it is highly similar to an FDA-approved biological product, known as a reference product, and has no clinically meaningful differences in terms of safety and effectiveness from the reference product.
- Minor differences in clinically inactive components are allowed. But there must be no clinically meaningful differences between the biosimilar and the

reference product it was compared to in terms of the safety, purity, and potency of the product.

- You may be familiar with the following biologics: Humira (adalimumab) for rheumatoid arthritis, Enbrel (etanercept) for rheumatoid arthitis, Remicade (infliximab) for Crohn's disease, Epogen (epoetin alpha) for anemia caused by chronic kidney disease, and Neupogen (filigrastim) for reducing risk of neutropenia while on chemotherapy.
- The medications listed below are biologics with available biosimilars:
    - Neupogen (filigrastim) – Biosimilar: Zaxio (Filgrastim-sndz)
    - Remicade (infliximab) – Biosimilar: Inflectra (infliximab-dyyb)
    - Enbrel (etanercept) – Biosimilar: Elrezi (etanercept-szzs)
    - Humira (adalimumab) – Biosimilar: Amjevita (adalimumab-atto).

Please rate each statement below from 1 (strongly disagree) to 5 (strongly agree).					
	Strongly Disagree				Strongly Agree
Q12a: I feel confident about prescribing (or administering) the appropriate biologic drug for my patient population.	1	2	3	4	5
Q12b: If the FDA has approved a biosimilar, I would offer it to my patients because I am confident it is safe and efficacious.	1	2	3	4	5
Q12c: I feel confident that the pharmacist will make the appropriate drug selection if an interchangeable drug is used without this information being communicated to me.	1	2	3	4	5
Q12d: I am more likely to select (or administer) a traditional drug to treat one of my patient's conditions than an interchangeable biologic product because I do not believe they are therapeutically equivalent.	1	2	3	4	5
Q12e: I do not perceive any barriers in appropriate selection of biologic drugs as pertains to my clinical practice.	1	2	3	4	5
Q12f: I believe we need a standard guideline for both doctors and pharmacists on the biosimilar substitution process.	1	2	3	4	5

Survey Adapted from Edward Li, PharmD "Biosimilars: An Assessment of Current Clinical Knowledge and Attitudes"

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