FEASIBILITY OF BIOSIMILAR INTEGRATION IN ONCOLOGY PRACTICE

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ABSTRACT

The therapeutic value of biologics is of extreme importance in the treatment of most major cancers. Biologics account for half of the oncologic pharmacology market. As the population of the United States ages, the demand for biologics is expected to increase. The future supply of biologics may be prohibited by cost. Biosimilar biologics are highly similar to existing Food and Drug Administration-licensed biologics and have the potential to meet biological demand. Market introduction of biosimilars at a lower cost than reference biologics creates an opportunity for reducing the nation's financial burden. Despite the obvious gains from biosimilar use, adoption into clinical practice continues to lag. Numerous factors, including a lack of education on the part of prescribers, continue to hinder the widespread adoption of biosimilars into practice. The purpose of this integrative review is to examine the evidence surrounding biosimilar determination and ascertain if adult patients diagnosed with cancer can be treated with biosimilars as compared to reference biologics without a compromise in safety and efficacy throughout the course of therapy.

Keywords: biosimilars, oncology biosimilar, biosimilarity, biologics

Dedication

I wish to dedicate this integrative review to two people without whom its completion would not be possible. First, to my husband, Jim. From the beginning, you served as the inspiration for betterment. Your personal sacrifices in the name of support will never be forgotten. Even in your final moments, your words were purposefully chosen as a means for thrusting me forward and ensuring that I completed this project. I will forever remain in your debt. Until then…

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Anti-Drug Antibodies (ADAs)

Biologics Price Competition and Innovation Act (BPCI Act)

Complete Response Rate (CRR)

Food and Drug Administration (FDA)

Hazard Ratio (HR)

Institutional Review Board (IRB)

Integrative Review (IR)

Neutralizing Drug Antibodies (NDAs)

Objective Response Rate (ORR)

Overall Survival (OS)

Pathological Complete Response Rate (pCR)

Pharmacodynamic (PD)

Pharmacokinetic (PK)

Post-Translational Modifications (PTMs)

Progression Free Survival (PFS)

Randomized Controlled Trials (RCTs)

Risk Difference (RD)

Risk Ratio (RR)

FEASIBILITY OF BIOSIMILAR INTEGRATION IN ONCOLOGY PRACTICE

Oncology practice is highly dependent on the use of biologics, which account for half of the oncologic pharmacology market (Konstantinidou, 2020). As the population ages and cancer prevalence increases, the demand for life-saving biologic therapeutics is expected to increase. Notably, access to biologics may be prohibited by cost. Biosimilar biologics are highly similar to existing Food and Drug Administration (FDA)-licensed biologics (reference biologics) with no clinically meaningful differences in safety, purity, or potency as compared to reference products (FDA, 2015). Biosimilars are not generics, but like generic drugs, biosimilars are approved by an abbreviated regulatory pathway and are less expensive than reference products. Table 1 outlines the differences between biosimilars and generic drugs.

Biosimilar uptake is expected to provide cost-savings for patients, healthcare systems, and the nation. Cost-savings will improve patient access to life-saving biologic therapeutics with a resultant improvement in patient outcomes. By 2024, patents on eight major oncology biologics will expire (Pittman, et al., 2019). As patents for currently licensed reference biologics expire, the number of FDA-approved biosimilars is expected to increase. As of December 2020, 29 biosimilars have been approved by the FDA, many for use in the oncology setting (see Table 2) (FDA,2020). Despite the potential for reducing the financial burden on the nation's healthcare system,the availability of oncologic biosimilars has not been associated with the uniform adoption of biosimilars into clinical practice.

Clinical uptake of biosimilars has been hindered by confusion surrounding the abbreviated approval process for biosimilars. A demonstration of biosimilarity is dependent on comparative analytical data as opposed to the safety and efficiency data required for approval of

a reference biologic (FDA, 2015). This difference is poorly understood by oncology providers and limits the comfortable prescribing of biosimilars (Cook et al., 2019). Other factors that limit biosimilar utilization include immunogenicity concerns, issues related to the process of extrapolation, interchangeability, third-party reimbursement, and pricing. Patients may harbor concerns about safety and efficiency as well. Therefore, this integrative review (IR) will examine the empirical evidence surrounding oncology biosimilars to determine if the widespread adoption of biosimilars in clinical practice is feasible.

Defining Concepts and Variables

A biosimilar is a biological medicine that has highly similar properties to an already approved FDA biologic without any clinically meaningful differences in terms of the safety, purity, or potency of the product (FDA, 2017). The model for demonstrating biosimilarity can be framed from a stepwise approach. Key concepts in demonstrating biosimilarity include preclinical analytical comparability, demonstrating analytical similarity, non-clinical pharmacokinetic (PK)/pharmacodynamic (PD) toxicology assessments, human PK/PD toxicology assessments, and a phase III clinical assessment of biosimilar safety, efficacy, and immunogenicity (Markus et al., 2017).

Rationale for Conducting the Review

As the population ages, a significant rise in the number of cancer cases is expected. In 2021, the number of new cancer cases in the United States (US) is expected to approximate 1,898,160, or 5200 new cases per day (Siegel et al., 2021). A demand for efficacious oncology therapeutics will accompany the increase in cancer incidence. Advances in science, technology, and genomics make precision treatment possible and result in improved patient outcomes.

Biologic drugs play an important role in the precise treatment of malignancy, and the demand for access to life-saving biologic therapeutics is high and expected to increase.

Biologics were first approved for use in cancer treatment and supportive care in 1989. They are produced in living systems and purified in complex, multi-step processes, including recombinant DNA technology and controlled gene expression. Biologics are molecularly complex, difficult to characterize, and subject to changes in manufacturing conditions. Biologic proteins can be 1000 times larger than chemically synthesized, small-molecule drugs (Patel et al., 2018). The structural complexity of biologics is further defined by the primary, secondary, tertiary, and in some cases, the quaternary structure of the protein (Vulto & Jaquez, 2017). It is this complexity that makes it difficult to identically reproduce biologics.

Biologics are subject to post-translational modifications (PTMs) such as glycosylation, oxidation, phosphorylation, sulphation, lipidation, disulphide bond formation, and deamidation. These PTMs have the potential to impact the immunogenicity of biologics, thus creating concerns about biologic safety and efficacy (Declerck et al., 2016). PTMs can occur naturally or be introduced by the manufacturing process. The manufacturing process for biologics is challenging and batch-to-batch variability is the norm. This typically does not compromise the physical, chemical, biological, or microbiological properties that define biologics (Vulto & Jaquez, 2017). These properties are referred to as the critical quality attributes of the product.

Biologic approval begins with a biologic license application and is regulated under 21 CFR 600-680. Approval requires at least three phases of safety and efficacy trials for every indication in which licensure is sought (FDA, 2015). The complexity of biologic development and manufacturing is costly. Estimates for the costs of manufacturing a biologic are between $95 and $225 per gram (Roy, 2019). The demand for such innovation is logical, but availability may

be prohibited by cost. US expenditures for oncology medicines are largely driven by biologics and reached nearly $150 billion in 2018, a 12.9% increase from the previous year (IQVIA, 2019). Monoclonal antibodies alone account for 35% of US drug expenditures (Patel, 2018). The continued delivery of biologically based cancer treatment must be balanced against the economic limitations of the US healthcare system.

The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was enacted as part of the Affordable Care Act on March 23, 2010, as a national response to the real and anticipated economic burden created by the demand for and use of biologics. The act is predicated on the fact that patents for existing licensed reference biologics have or will expire. By 2023, the patents of approximately 20 biologics will expire (Konstantinidou et al., 2020). Just as the Drug Price Competition and Patent Restoration Act created an approval pathway for small molecule generic entrants and promoted competition between brand and generic manufacturers, the BPCI Act created an abbreviated licensure pathway (351(k)) for biological products shown to be biosimilar to or interchangeable with an FDA-licensed biological reference product in which the patent has expired (FDA, 2015). When the BPCI Act was passed, it was projected that the introduction of biosimilars at 20% to 30% lower costs would create competition among manufacturers of biologics, drive down biologics' cost, and improve patient access to needed biologic therapies (Nabhan et al., 2018).

The abbreviated approval process outlined by the BPCI Act focuses on criteria for demonstrating a high degree of similarity to a reference biologic and differs from traditional biologic endpoints. The establishment of biosimilarity involves an extensive characterization of the physiochemical and biological attributes of the biosimilar as compared to the reference biologic. Determining biosimilarity does not follow traditional new drug development but

depends on knowledge gained from an understanding of the reference product. The FDA recommends a stepwise approach including in vitro analytical testing, nonclinical comparative pharmacology testing, a toxicology assessment, PK/PD testing, and one or more clinical comparative studies to confirm the quality, safety, and efficacy of the product (Markus et al., 2017).

Demonstrating biosimilarity involves an assessment of clinical immunogenicity. The goal of an immunogenicity assessment is to uncover potential differences in human immune responses between the biosimilar and the reference biologic. Clinical comparative studies can address any residual uncertainty surrounding the biosimilar. Approval of a biosimilar means that "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components," and that "there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product" (FDA, 2015, p. 24).

As of December 2020, 29 biosimilars have been approved by the FDA for use, many in the oncology setting (see Table 2) (FDA, 2020). Biosimilars can provide significant savings for healthcare systems. It is predicted that the uptake of biosimilars will save the US $250 billion between 2014 and 2024 (Leber, 2018). Much of the enthusiasm and anticipated savings come from an examination of the European biosimilar market, where biosimilars were introduced in 2006 and have resulted in significant healthcare cost savings. Biologic savings depend on an uptake of biosimilars. Unlike Europe, where biosimilar uptake has been embraced, uptake in the US has moved at a slower pace. The low utilization of biosimilars prohibits the achievement of the policymakers' goals of increasing competition, driving down prices, and improving patient access to biologics.

Factors contributing to the delayed uptake of biosimilars in the US include ongoing patent litigation and rebate schemes (Leber, 2018). A key reason for the delayed adoption of biosimilars into clinical practice and clinical guidelines is provider resistance, largely driven by a lack of provider knowledge and a need for education about the approval process, safety profiles, extrapolation, and interchangeability. A survey by Cook et al. (2019) among 77 oncology clinicians found that understanding of biosimilars is low, and educational needs are high. Provider fears also hinder the use of biosimilars. A commonly cited concern is the lack of traditional safety and efficacy data generated by clinical trials and real-world data. Other concerns include the potential for immunogenicity, misgivings about extrapolation, and a perceived loss of control if biosimilars become interchangeable (Pittman, 2019). Providing education and addressing provider fears is an important step in increasing the use of biosimilars. In fact, clinicians indicated a 40% increase in the likelihood of prescribing a biosimilar given adequate data on biosimilar safety and efficacy (Cook et al., 2019). Alleviating provider fears will require an understanding of biosimilar determination and a review of the evidence supporting the incorporation of biosimilars into routine clinical practice.

Purpose and/or Review Question

Biologics play an important role in the treatment of malignancy. An aging population and an increase in the number of newly diagnosed cancers are accompanied by an increase in the demand for life-saving biologics. Biologics are expensive and create a chronic burden for the US healthcare system. Guaranteed access to therapeutic biologics is threatened by a lack of cost containment. Biosimilars are biologics that are highly similar to FDA approved reference biologics. As a result of the approval process, biosimilars are introduced at a lower cost than reference biologics with resultant savings to healthcare stakeholders and improved patient access

to biologics. Despite availability, the uptake of biosimilars into clinical practice is suboptimal. A lack of awareness among oncology providers concerning evidence for the safe incorporationof biosimilars into clinical practice limits biosimilar utilization. If continued, the lack of utilization will result in forfeiture of the biosimilar space and the loss of billions in healthcare savings.

The purpose of this IR is to examine the evidence surrounding the biosimilar determination of available oncology therapeutics. This review should help determine if the adoption of biosimilars to formulary and into clinical practice is feasible without a compromise in safety or efficacy as compared to reference products. This IR addresses the following clinical question: can adult patients diagnosed with cancer be treated with biosimilars as compared to reference biologics without a compromise in safety and efficacy over the course of therapy?

Inclusion and Exclusion Criteria

This review primarily focuses on quantitative evidence as it relates to demonstrating biosimilarity. Inclusion criteria include systematic reviews, meta-analyses, and randomized controlled trials (RCTs). The adult age range is applied. Outcomes of interest include supportive care and therapeutic oncology biosimilars. Non-English studies and those failing to report comparative outcomes are excluded.

Conceptual Framework

The framework for this IR is supported by the methodology of Whittemore and Knafl (2005). The methodology allows for the inclusion of experimental and non-experimental research. This review is based on experimental research. The initial stage of any review is problem identification. This review addresses the safe incorporation of biosimilars into oncology

practice. Problem identification is followed by a literature search, data synthesis, and data presentation. This review follows these steps in accordance with the proposed methodology.

COMPREHENSIVE AND SYSTEMATIC SEARCH

Search Organization and Reporting Strategies

The library staff at Liberty University was consulted prior to the initiation of the literature review. In this IR, the literature review was conducted in accordance with the methodology proposed by Whittemore and Knafl (2005). Whittemore and Knafl (2005) recommend that the literature search for an IR be clearly documented and include search terms, databases used, and the inclusion and exclusion criteria for determining relevant primary sources. Whittemore and Knafl (2005) point out that a gold standard for evaluating and interpreting literature quality does not exist. This IR uses levels of the evidence outlined by Melnyk and Fineout-Overholt (2015) for critical appraisal of the literature.

Terminology

A systematic search was conducted using several databases. The CINAHL database, maintained by the EBSCO host platform, was selected due to its comprehensive index of nursing research and information and access to peer-reviewed journals. The Cochrane Library database, operated by the CRD, EBSCO, OVID, and Wiley platforms, allowed for a search of systematic reviews. Medline (Proquest) was selected because this database includes the platforms of PubMed and the Web of Science. The Nursing & Allied Health Database provided indexed journal content from the nursing literature and other related disciplines using the Proquest platform. Additionally, Clinicaltrials.gov was selected as a privately and publicly funded database of clinical studies conducted from around the world. Assistance to full-text articles and search assistance was provided by the research department of Liberty University.

MANAGING THE COLLECTED DATA

For this IR, the keywords used to conduct a comprehensive search of the databases were "biosimilars" and "oncology." Inclusion criteria were: (a) scholarly works published in a peer-reviewed journal, (b) works written in English, (c) works published within the last five years, and (d) quantitative studies consisting of systematic reviews, meta-analyses, RCTs. Exclusion criteria were: (a) qualitative studies, (b) opinion articles, and (c) articles published before January 1, 2015.

The initial search resulted in a sample of 193 articles. The CINAHL search was conducted using the Boolean/Phrase function for the selected keywords, and 90 studies were identified. An advanced search within the Cochrane Library found five articles. Medline (ProQuest) was searched using the advanced function and the qualifying peer-review box. Forty-two studies were isolated. The Nursing & Allied Health database search was conducted in the advanced mode with the selection of the peer-reviewed function, and 50 articles were identified.A search of the Clinicaltrials.gov website using the advanced mode and application of filters for oncology, biosimilars, and interventional studies produced six studies for review.

QUALITY APPRAISAL

The final sample for this IR was selected after the application of inclusion and exclusion criteria. Twenty-seven studies remained. Once duplicates were removed, 20 studies were available for review. Twenty remaining articles were assessed for levels of evidence, sources of bias, and the extent to which an FDA-approved endpoint was measured in determining biosimilarity. Articles were also graded for relevance on a two-point scale (high or low). Fifteen studies remained for inclusion in this IR (see Appendix A). The appraisal tool for the studies will be reviewed below.

Sources of Bias

Identifying bias starts by examining each study for potential sources of bias. The focus on bias provides internal validity (Remington, 2020). Fifteen studies included in this IR were examined for potential bias by examining the selection of participants, quality of measurements, rate of attrition, and symmetry of performance. Study limitations are outlined in Appendix A. Overall, some bias may be present across studies due to small sample size, varying outcome measures, and statistical underpowering. Bias may also occur due to the selection of only high-level evidence.

Internal Validity

Internal validity occurs when the results of the study approximate the truth (Remington, 2020). The validity of the systematic reviews and meta-analyses was determined by assessing the comprehensiveness of included sources and the degree to which each source was appraised. The internal validity of RCTs was considered good if the trials outlined adequate randomization, comparison groups, measurement criteria with instrument validity, and outcomes. Bias, as outlined above, was also considered.

Appraisal Tool

A gold standard for evaluating and interpreting literature quality does not exist (Whittemore & Knafl, 2005). Nonetheless, any evidence included in an IR should be critically evaluated (Remington, 2020). This IR uses levels of the evidence outlined by Melnyk and Fineout-Overholt (2015) for critical appraisal of the literature. Levels range from I-VII. Level I evidence is supported by systematic reviews or meta-analyses of RCTs or evidence-based clinical practice guidelines based on systematic reviews. Level II evidence comes from a well-designed RCT. Level III depends on a controlled trial without randomization (quasi-experimental

study). Level IV requires a single nonexperimental study (case-control, correlational, or cohort study). Level V is based on a systematic review of descriptive and qualitative studies. Level VI involves a single descriptive or qualitative study. Level VII entails an opinion of authorities and/or reports of expert committees.

Applicability of Results

The applicability of the studies included in the IR was assessed using the appraisal tool described above. Each study has been appraised with results highlighted in the appraisal matrix (see Appendix A). Categories included in the matrix to help support the credibility of the data analysis, and findings are as follows: identifying article information, study purpose, characteristics of the sample, methods, level of evidence, study limitations, and application of evidence.

Reporting Guidelines

The current lack of a standard for IR reporting does not negate the importance of following an established guideline when reporting the findings of an IR. A few guidelines are available including the PRISMA mode, and the one followed in this IR, as outlined by Whittenmore and Knafl (2005). The methodology allows for the inclusion of experimental and non-experimental research; this review is based on experimental research. The initial stage of any review is problem identification. This review addresses the safe incorporation of biosimilars into oncology practice. Problem identification is followed by a literature search, data synthesis, and data presentation. This review follows these steps in accordance with the proposed methodology.

DATA ANALYSIS AND SYNTHESIS

Data Analysis Method

The data analysis method for this IR followed the recommendations of Whittenmore and Knafl (2005). A constant comparison methodology was used. Initially, all data were compared item by item. Similar data were grouped together for further comparison. Categories were coded to allow for further synthesis and analysis. Categories were subdivided into supportive biosimilars and therapeutic biosimilars. Additional subclassifications included analytical determination, clinical comparative determination, and switch determination.

Once grouped, the data was analyzed for patterns, themes, and relationships. The data was assessed for conflicting evidence. Studies were grouped according to commonalities and generalizations of each group formulated. Formulations were compared and conclusions developed based on the literature.

Descriptive Results

Review studies comprised five systematic reviews, two meta-analyses, and eight RCTs. Two of the systematic reviews were concerned with switching from reference biologics to biosimilars. The remaining reviews focused on the overall safety and efficacy of biosimilars. The two meta-analyses examined evidence for the incorporation of trastuzumab biosimilars and growth-factor biosimilars into clinical practice. Seven of the RCTs were double-blind studies with one single-blind, single-dose evaluation study. Four of the trials were conducted in breast cancer patients, two in patients with lymphoma, and one trial in healthy male subjects. Oncology biosimilar drugs reviewed in the studies included those as comparable to reference products for bevacizumab, pegfilgrastim, rituximab, and trastuzumab.

The systematic review by Barbier et al. (2020) synthesized the available data on switching between reference biologics and biosimilars. Studies included 21,000 patients and were composed of RCTs and real-world evidence. Both single and multiple switch studies were

examined and included filgrastim, rituximab, and trastuzumab. Limitations of the review included a lack of robust design for most evaluated studies and that the short-term follow-up for most studies limits the detection of delayed adverse events. The main strength of the study was the coverage of multiple molecules across a variety of settings. Overall, the data provided no indication that switching from a refence biologic to a biosimilar was related to any compromise in safety, efficacy, or immunogenicity.

Cohen et al. (2018) reviewed 90 switching studies (14,224 individuals) to determine if switching from a reference biologic to a biosimilar would result in altered clinical outcomes, enhanced immunogenicity, or a compromise in safety or efficacy. The review was limited by inclusion of only one oncology supportive care biologic, filgrastim. Additionally, most studies were descriptive and not powered to detect switch-related differences. Across studies, no new safety signals were reported and no compromise in safety or efficacy was observed.

Coory and Thornton (2019) performed a systematic review of eight publications for seven randomized endpoints and five trastuzumab biosimilars to assess the evidential role of randomized clinical endpoint studies in the approval of trastuzumab biosimilars. Although variability in methods used by individual studies was a weakness, the authors concluded, according to GRADE, that the totality-of-evidence for trastuzumab biosimilar approvals was less dependent on end points and more dependent on in vitro analytic characterization of the biosimilar. Furthermore, this characterization was sensitive enough to detect any clinically meaningful differences in reference biologics and the corresponding biosimilar.

Yang and colleagues (2019) synthesized current evidence on the efficacy and safety of monoclonal antibodies relative to their refence biologics among cancer patients. Twenty-three RCTs were evaluated, eight with biosimilar rituximab, six with biosimilar bevacizumab, and

nine with biosimilar trastuzumab. Based on the pooled binary outcomes using risk ratio with 95% confidence intervals (CIs), continuous outcomes using weighted mean difference with 95% CIs, and time-to-event outcomes using hazard ratios (HRs), the existing evidence suggested a high degree of comparable efficacy and safety between reference monoclonal antibodies and biosimilar monoclonal antibodies. The strength of the study is that it was the first to comprehensively evaluate all types of monoclonal antibody biosimilars to reference biologics. The review was limited by the lack of data for outcomes such as overall survival (OS) and progression-free survival (PFS). It should be noted that these outcomes are not required for a demonstration of biosimilarity. Further observational studies incorporating these outcomes will help to confirm the safety of biosimilars.

In a meta-analysis of randomized clinical trials in breast cancer patients, Botteri et al. (2018) compared the clinical efficacy and safety of approved or proposed supportive care biosimilar filgrastim or pegfilgrastim with the reference products. Eight RCTs with a total of 1,843 breast cancer patients were included in the review. Three studies were from Germany, two from the US, two from Brazil, and one from South Korea. Filgrastim was the reference product in five studies and pegfilgrastim in three studies. Based on an evaluation of the mean difference in duration of severe neutropenia, differences in depth of absolute neutrophil count nadir, time to neutrophil recovery, and incidence of febrile neutropenia, no significant differences were seen in clinical efficacy or safety between biosimilar and reference filgrastim and pegfilgrastim. The review was limited by the small number of studies included. The review was the first meta-analysis of supportive care biosimilar medicines.

Using a network meta-analysis, Mengato et al. (2019) compared the HR value of PFS for patients treated with reference trastuzumab to approved biosimilar trastuzumab MYL-14010.

Despite the limitation of the review of a specific trastuzumab biosimilar, MYL-14010 was found to be as effective as its original reference product based on an analysis of the HR values for biosimilar products, the reference product, and the standard of care.

In a comparison of proposed biosimilar LA-EP2006 with reference pegfilgrastim, Blackwell et al. (2016) randomized 308 patients with early-stage breast cancer to LA-EP2006 or reference pegfilgrastim following chemotherapy. The primary endpoint of the study was the duration of severe neutropenia during cycle 1 with equivalence confirmed if 90% and 95% confidence intervals were within a 1-day margin. The duration of severe neutropenia was equivalent between groups, and no differences were seen in terms of safety and efficacy. No treatment-related binding or neutralizing antibodies against either product were detected during the study. This provided strength for generalizing the findings to patients receiving chemotherapy regardless of cancer type.

A single-blind, single-dose study by Hanes et al. (2017) examined the PK equivalence of proposed biosimilar ABP980 and trastuzumab in 157 healthy male subjects. Following a single dose of 6 mg/kg of intravenous ABP980 or FDA-licensed trastuzumab, area under the serum concentration-time curve from time 0 to infinity and maximum observed serum concentration were measured as a means of establishing equivalence of the products. Using a geometric mean ratio and 90% CI, the study demonstrated the PK similarity of ABP980 to reference trastuzumab. No subjects developed binding or neutralizing anti-drug antibodies by the end of the study.

The LILAC study addressed the safety and efficacy of ABP980 compared with reference trastuzumab in women with human epidermal growth factor-positive (HER2+) early breast cancer. Seven hundred twenty-five women aged 18 years or older and eligible to receive chemotherapy were randomized to ABP980 or reference trastuzumab. Co-primary endpoints

were risk difference (RD) and risk ratio (RR) of pathological complete response in breast tissue and axillary lymph nodes. Based on local laboratory review of tumor samples, the lower bounds of the 90% CIs showed non-inferiority. A central lab analysis indicated similar efficacy and safety for ABP980 and reference trastuzumab. The study may be limited by the fact that clinical tumor response can vary, and there was no validated standard to differentiate between two similar products (Minckwitz et al., 2018). The central lab confirmation was a study strength.

The trastuzumab biosimilar PF-05280014 plus paclitaxel was compared to reference trastuzumab plus paclitaxel for HER2+ metastatic breast cancer by Pegram et al. (2018) in a randomized, double-blind study of 707 participants with at least one measurable confirmed metastatic lesion. Participants received standard dose therapy. The primary endpoint was objective response rate (ORR) by week 25 based on blinded central radiology review. The ORR was 0.940, and the 95% CI fell within the pre-specified equivalence margin of 0.80-1.25. The study concluded that when given as a first-line treatment for HER2+ metastatic breast cancer, PF-05280014 plus paclitaxel demonstrated equivalence to reference trastuzumab plus paclitaxel in terms of ORR. A strength of the study was that ORR is one of the FDA accepted end points for demonstrating biosimilarity. The randomized double-blind design and blinded independent radiograph review were also strengths. A limitation of the study was that it did not evaluate the current standard of care in the metastatic setting which is dual HER2 blockade with trastuzumab and pertuzumab.

In a randomized, double-blind, parallel-group study, PF-06439535 (a bevacizumab biosimilar) was compared with reference bevacizumab, both in combination with paclitaxel and carboplatin, as first-line treatment for 719 patients with advanced non-squamous, non-small-cell lung cancer. The primary endpoint was ORR in accordance with RECIST criteria confirmed by

week 25. Patients treated with the biosimilar achieved an ORR of 44.6% as compared to patients treated with reference bevacizumab that achieved a 45.3% ORR. The final data after study completion noted no difference in terms of the safety and efficacy of the two products. There were no notable differences in PFS or OS. The strength of the study was its design, including the accepted endpoint for demonstrating biosimilarity. The study was limited by the fact that 85.4% of enrolling countries are outside the US where chemotherapy availability can vary (Reinmuth et al., 2019).

A randomized, double-blind, efficacy and safety study of PF-05280586 (biosimilar rituximab) compared with reference rituximab was conducted in 394 patients with previously untreated CD20-positive, low-tumor-burden follicular lymphoma. Patients were randomized to receive 375 mg/m2 of either product on days 1, 5, 8, and 22. The primary endpoint was ORR assessed at week 26. To establish equivalence, the two-sided 95% CI for the difference in ORR between the groups had to fall within the prespecified margin of ± 16%. The secondary endpoints of PFS, CR, safety, immunogenicity, PKs and PDs were included. The study demonstrated therapeutic equivalence between the two products across endpoints. A potential limitation of the study, although not required by the FDA, was that it failed to show equivalence in every indication for which rituximab is approved. Additionally, subjects received only four doses of therapy as opposed to the standard eight doses (Sharman et al., 2020).

Viswabandya et al. (2019) conducted a randomized, double-blind, PK equivalence trial comparing the biosimilar rituximab (DRL-rituximab) with reference rituximab (MabThera) in patients with diffuse large b-cell lymphoma. A total of 151 untreated patients eligible to receive CHOP chemotherapy were randomized to CHOP with the biosimilar or CHOP with the reference product. Equivalence was based on the primary endpoint of PKs following cycle one. Secondary

endpoints were ORR at cycle six and event-free survival and OS at week 87. Rates of b-cell depletion were measured. Investigators found no difference between the compounds in terms of PKs, PDs, safety, and immunogenicity. The study was conducted in a single country. The design provided strength. The sample size may have limited statistical power.

Xavier et al. (2018) conducted a phase III, randomized, double-blind study comparing the efficacy, safety, and immunogenicity of SB3 (trastuzumab biosimilar) and reference trastuzumab for 800 patients treated with neoadjuvant therapy with HER2+ early breast cancer receiving adjuvant chemotherapy. The primary endpoint was breast pathological complete response rate (pCR). Equivalence was set if the 95% CI ratio was within the predefined margin of 0.785 to 1.546 or the CI was declared within ± 13%. Secondary endpoints included complete response rate (CR), ORR, event-free survival, OS, PKs, and immunogenicity. Equivalence for efficacy was demonstrated based on the primary endpoint between both products. Antibody development was not observed. Strengths for the study included the study design and inclusion of OS as a secondary endpoint.

Synthesis

The types of biosimilars addressed for use in oncology include bevacizumab, pegfilgrastim, rituximab, and trastuzumab. Eight RCTs comparing the use of one of the above biosimilars to a reference product found no difference in the efficacy, safety, and immunogenicity of the products based on the varying clinical endpoints of ORR, pCR, PKs, RD or RR (Blackwell et al., 2016; Hanes et al., 2016; Minckwitz et al., 2018; Pegram et al., 2018; Pivot et al., 2018; Reinmuth et al., 2019; Sharman et al., 2020; Viswabandya et al., 2019). The meta-analysis by Yang et al. (2019) also determined no difference in the efficacy, safety, and immunogenicity among eight biosimilar and reference monoclonal antibodies. Although not

required to demonstrate biosimilarity, five studies compared survival either by measuring PFS or OS and determined no differences in the two among patients treated with a biosimilar versus a reference product (Mengato et al., 2019; Pivot et al., 2018; Reinmuth et al., 2019; Sharman et al., 2020; Viswabandya et al., 2019).

Two meta-analyses examined the concept of switching from a reference biologic to a biosimilar for filgrastim, rituximab, and trastuzumab. Switching products was not associated with a compromise in outcomes, efficacy, safety, or immunogenicity (Cohen et al., 2018; Coory & Thornton, 2019). The meta-analysis by Botteri et al. (2018) and the clinical comparative study by Blackwell et al. (2016) found no differences in the duration of severe neutropenia, safety, or immunogenicity among supportive care biosimilars (filgrastim; pegfilgrastim) versus the reference products.

Ethical Considerations

This project was submitted to the Liberty University Institutional Review Board (IRB). The review board granted an exempt, no human subject research status on May 27, 2021. A copy of the IRB decision can be found in Appendix B. Biomedical research training has been completed through the Collaborative Institutional Training Initiative (see Appendix C).

Timeline

The timeline for this project includes the following phases: pre-proposal, project proposal submission, and final project submission. Final project defense took place on July 22, 2021.

DISCUSSION

Prior to routinely introducing biosimilars into oncology clinic practice, it is necessary to establish that adult patients diagnosed with cancer can be treated with biosimilars as compared to reference biologics without a compromise in safety and efficacy over the course of therapy.

Demonstrating the safety and efficacy of biosimilars requires that the biosimilar product be highly similar to its reference product. The evidence supporting similarity is predicated on robust data from analytical, PK/PD, nonclinical, and clinical studies as outlined in the abbreviated approval process for biosimilars (Mengato et al., 2019). Clinical studies are important for revealing any clinically meaningful differences between the biosimilar and the reference biologic in terms of safety, efficacy, and immunogenicity.

High-quality evidence from four systematic reviews/meta-analyses suggests that biosimilar trastuzumab used as treatment for breast cancer (metastatic, neoadjuvant, adjuvant) is equivalent to reference trastuzumab in terms of overall response rate (ORR), hazard ratio (HR), progression free survival (PFS), and safety. Four RCTs comparing biosimilar trastuzumab to the reference product show similar PK profiles (healthy males) as well as similar safety and efficacy in terms of ORR, PFS, overall survival (OS), duration of response (DOR), and pathologic complete response rate (pCR) in women with breast cancer. Two of the RCTs focus on biosimilar ABP980 which is now approved in the US. ABP980 demonstrated PK equivalency and similar efficacy as compared to the reference product. In studies evaluating ABP980, anti-drug antibodies (ADAs) were not found.

High-grade evidence from two systematic reviews indicates that biosimilar bevacizumab is highly similar in terms of safety and efficacy as compared to the reference product when used in combination with chemotherapy in patients with lung and colon cancer. PK values are equivalent between the two products. No new safety signals or immunogenicity concerns are identified in comparing products. A RCT comparing biosimilar and refence bevacizumab in combination with chemotherapy in lung cancer patients documents similarity of the products in terms of ORR and PFS among group participants.

High-grade evidence from two systematic reviews establishes a high degree of similarity between reference rituximab and biosimilar rituximab in terms of PK/PD profiles, efficacy, safety, and immunogenicity using ORR as the clinical endpoint. Testing was conducted in populations with b-cell disorders such as lymphoma and chronic lymphocytic leukemia. Two RCTs confirm similar safety and efficacy of biosimilar rituximab as compared to reference rituximab in terms of ORR, PFS, OS, and DOR. Biosimilar and reference rituximab have similar rates of b-cell depletion.

Granulocyte colony-stimulating factors (pegfilgrastim and filgrastim) are routinely used to prevent neutropenia and support cancer patients undergoing myelosuppressive chemotherapy (Botteri et al., 2018). Biosimilar versions of these support factors are available in the US. Adoption of supportive care medicines continues to lag due to clinician concerns and lack of safety awareness. High-grade evidence from a systematic review and a meta-analysis of supportive care biosimilars among different populations demonstrates highly similar efficacy and safety outcomes for supportive care biosimilars as compared to reference products.

Switching patients from a reference product to a biosimilar has created concern among clinicians regarding the potential for immunogenicity and the development of ADAs or neutralizing drug antibodies (NDAs) secondary to the switching process. Analysis of data from this IR involving systematic reviews evaluating switch studies in over 21,000 patients determined that switching from a reference product to a biosimilar product is not associated with a compromise in drug safety or efficacy. The development of ADAs or ANAs is not an issue when switching from a reference product to a biosimilar and vice versa.

Based on an analysis of the data at hand, the abbreviated pathway for biosimilar approval is scientifically sound. The approval process allows for the establishment of biosimilarity and a

determination that biosimilars are as safe and efficacious as reference biologics. The pooled analysis suggests that incorporating biosimilars into oncology clinical practice can be done safely without concerns for compromised efficacy. Using a biosimilar or switching to a biosimilar is not associated with immunogenicity issues. Although biosimilarity is established early in the approval pathway by analytical studies, data from the phase III clinical comparative study is essential to examine when making a choice to incorporate biosimilars into oncology clinical practice.

Limitations

This IR has several limitations. The simplicity of the search terms “biosimilars” and “oncology” may have led to missing data. A methodological limitation may exist in that only high-quality evidence is presented. Data analysis does not include all US approved biosimilars. Outcomes varied across studies. Biosimilarity is evaluated in mainly breast, lung, and lymphoma populations, which make the findings in this IR not generalizable to other populations.

Implications for Practice/Future Work

The incorporation of biosimilars into oncology clinical practice can be safely adopted with the bonus of cost savings across the healthcare sector. Much of the adoption may be influenced by institutional formularies and third-party payer requirements. Advance practice providers (APPs) must seek opportunities to participate in formulary selection and can serve as sources for reviewing evidence that supports biosimilar adoption. APPs can provide education for key stakeholders and patients. APPs can serve at the local, state, or federal levels to provide guidance regarding policies that regulate biosimilarity and interchangeability. APPs must understand the value and interpretation of clinical comparative studies and participate as investigators in the biosimilar clinical trial process.

Dissemination

The findings of this IR will be submitted to a peer-reviewed journal, the target journal is *The Journal of the Advanced Practitioner in Oncology.* Submissions are required in APA format. The journal is available online and targets all advanced practice providers, including pharmacists. An abstract will be submitted to JADPROLive 2021 ahead of an anticipated poster presentation.

CONCLUSION

As the US population ages and an increasing number of patients are diagnosed with cancer, the demand for therapeutic biologics is expected to increase. The escalating costs of biologics may hinder patient access to them, thereby negatively impacting patient outcomes. The BPCI Act provides a sound regulatory approval process for highly similar biologics (biosimilars) that can be introduced at a lower cost, thereby increasing patient access to needed biologics. Systematic reviews, meta-analyses, and RCTs evaluated in this review find no differences in terms of safety, efficacy, and immunogenicity of biosimilars as compared to reference supportive care and therapeutic biologics. These findings support that biosimilars can be safely adopted into oncology clinical practice. Ongoing studies and new biosimilar approval studies must continue to confirm this conclusion.

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Table 1

Biosimilar and Generic Drug Comparison

	Biologic	**Generic**
Type	Protein-based	Chemically based
Production	Living cell lines	Chemical synthesis
Size	Large (1000 x)	Small
Molecular Weight	High	Low
Structure	Complex/heterogeneous	Simple/defined
Characterization	Full characterization not possible	Complete
Immunogenicity	Immunogenic	Low potential

Note: Adapted from "Biologics and biosimilars: Role in modern pharmacotherapy and importance of pharmacovigilance," by R. R. Alachandani, B. M. Sattigeri, and P. S. Karelia. *International Journal of Research in Medical Sciences, 2*(2), 382-386. Copyright 2014 Alamchandani RR et al.

Table 2

List of Currently Approved Biosimilars

Biosimilar	Approval Date
Abrilada (adalimumab-afzb)	November 2019
Amjevita (adalimumab-atto)	September 2016
Avsola (infliximab-axxq)	December 2019
Cyltezo (adalimumab-adbm)	August 2017
Erelzi (etanercept-szzs)	August 2016
Eticovo (etanercept-ykro)	April 2019
Fulphila (pegfilgrastim-jmdb)	June 2018
Hadlima (adalimumab-bwwd)	July 2019
Herzuma (trastuzumab-pkrb)	December 2018
Hulio (adalimumab-fkjp)	July 2020
Hyrimoz (adalimumab-adaz)	October 2018
Inflectra (infliximab-dyyb)	April 2016
Ixifi (infliximab-qbtx)	December 2017
Kanjinti (trastuzumab-anns)	June 2019
Mvasi (bevacizumab-awwb)	September 2017
Nivestym (filgrastim-aafi)	July 2018
Nyvepria (pegfilgrastim-apgf)	June 2020
Ogivri (trastuzumab-dkst)	December 2017
Ontruzant (trastuzumab-qyyp)	January 2019
Renflexis (infliximab-abda)	May 2017
Retacrit (epoetin alfa-epbx)	May 2018
Riabni (rituximab-arrx)	December 2020
Ruxience (rituximab-pvvr)	July 2019
Trazimera (trastuzumab-qyyp)	March 2019
Truxima (rituximab-abbs)	November 2018
Udenyca (pegfilgrastim-cbqv)	November 2018
Zarxio (filgrastim-sndz)	March 2015
Ziextenzo (pegfilgrastim-bmez)	November 2019
Zirabev (bevacizumab-bvzr)	June 2019

Note: Adapted from "Biosimilars," *Food and Drug Administration*, https://www.fda.gov/drugs/biosimilars/biosimilar-product-information. Copyright 2021 by the Food and Drug Administration.

Appendix A

Levels of Evidence

Article Title, Author, etc. (Current APA Format)	Study Purpose	Sample (Characteristics of the Sample: Demographics, etc.)	Methods	Study Results	Level of Evidence (Use Melnyk Framework)	Study Limitations	Would Use as Evidence to Support a Change? (Yes or No) Provide Rationale.
Barbier et al. (2020). The efficacy, safety, and immunogenicity of switching between reference biopharmaceuticals and biosimilars: A systematic review. *Clinical Pharmacology & Therapeutics*, *108*(4), 734-755. https://dx.doi.org/10.1002/cpt.1836	To synthesize the available data on switching from a reference product to a biosimilar and assess if switching affects efficacy,	178 studies comprised of RCTs and real world evidence. Studies included 21,000 switched patients.	A systematic literature review was carried out up to the 19th of June 2018 in the biomedical databases Embase, Medline, Cochrane and Web of Science. Search results were manually screened based on predefined inclusion and	Switching from a reference biologic to a biosimilar does not result in any major efficacy, safety, or immunogenicity issues.	Level 1: Systematic review of RCTs and real-world evidence	Short-term follow-up of studies does not provide sensitivity to detect rare AEs.	Yes. Would only use it to support a change in the biosimilars studies in the review.

Article Title, Author, etc. (Current APA Format)	Study Purpose	Sample (Characteristics of the Sample: Demographics, etc.)	Methods	Study Results	Level of Evidence (Use Melnyk Framework)	Study Limitations	Would Use as Evidence to Support a Change? (Yes or No) Provide Rationale.
	safety, or immunogenicity outcomes.		exclusion criteria.				
Blackwell et al. (2016). A comparison of proposed biosimilar LA-EP2006 and reference pegfilgrastim for the prevention of neutropenia in patients with early-stage breast cancer receiving myelosuppressive adjuvant or neoadjuvant chemotherapy: Pegfilgrastim randomized oncology (supportive care) trial to evaluate comparative treatment (PROTECT-2), a phase III, randomized, double-blind trial. *The Oncologist, 21,* 789-794.	A confirmatory efficacy and safety study designed to compare proposed biosimilar LA-EP2006 with reference pegfilgrastim in early-stage	308 women >/= 18 years of age with histologically proven early-stage breast cancer eligible for neoadjuvant or adjuvant treatment with docetaxel, doxorubicin	Patients randomized 1:1 to LA-EP2006 or reference pegfilgrastim (Neulasta) on day 2 of each cycle of therapy. Primary endpoint: duration of severe neutropenia during cycle 1 with equivalence	Duration of severe neutropenia was equivalent between groups in cycle one. Safety profiles were also similar between groups.	Level 2: RCT	May be difficult to compare patient-reported AEs across trials due to differences in recording AEs in actual clinical settings.	Yes. Evidence supports the use of the biosimilar Neulasta following chemotherapy that results in high rates of febrile neutropenia,

Article Title, Author, etc. (Current APA Format)	Study Purpose	Sample (Characteristics of the Sample: Demographics, etc.)	Methods	Study Results	Level of Evidence (Use Melnyk Framework)	Study Limitations	Would Use as Evidence to Support a Change? (Yes or No) Provide Rationale.
http://dx.doi.org/10.1634/theoncologist.2016-0011	breast cancer patients receiving adjuvant or neoadjuvant myelosuppressive chemotherapy.	, cyclophosphamide chemotherapy. ECOG PS 0-2. Disease stage I-III.	confirmed if 90% and 95% CIs were within pre-defined margins.	No ANAs were detected.			independent of tumor type.
Botteri et al. (2018). Comparing granulocyte colony-stimulating factor filgrastim and pegfilgrastim to its biosimilar in terms of efficacy and safety: A meta-analysis of randomized clinical trials in breast cancer patients.	To compare the clinical efficacy and safety of approved or	8 RCT studies published between 2008 and 2016. 1843 patients	Literature search using Pubmed/Medline using serach strings: Filgrastim breast cancer and	No statistically significant difference in duration of severe neutropenia between	Level 1: Meta-analysis of RCTs.	Small number of studies included in the analysis.	Yes. Results support the use of biosimilar G-CSF for supportive care in

Article Title, Author, etc. (Current APA Format)	Study Purpose	Sample (Characteristics of the Sample: Demographics, etc.)	Methods	Study Results	Level of Evidence (Use Melnyk Framework)	Study Limitations	Would Use as Evidence to Support a Change? (Yes or No) Provide Rationale.
European Journal of Cancer, 89, 49-55. https://doi.org/10.1016/j.ejca.2017.10.034	proposed G-CSF biosimilars (filgrastim or pegfilgrastim) with reference G-CSF in breast cancer patients.	with breast cancer included.	Pefgilgrastim breast cancer. Primary end point duration of severe neutropenia during cycle 1. Secondary end point safety. Statistical analysis per SAS software version 9.4.	reference and biosimilar G-CSF. No safety differences between reference and biosimilar G-CSF			patients receiving myelo-suppressive therapy. Has clinical implications for the choice of G-CSF to be used in clinic and provides for cost savings.
Cohen, et al. (2018). Switching reference medicines to biosimilars: A systematic	To determine if	90 switching studies	Systematic search using Medline and	The risk of immunogenicity-related	Level 5: Systematic	Variability in methods used by	Yes. It would be

Article Title, Author, etc. (Current APA Format)	Study Purpose	Sample (Characteristics of the Sample: Demographics, etc.)	Methods	Study Results	Level of Evidence (Use Melnyk Framework)	Study Limitations	Would Use as Evidence to Support a Change? (Yes or No) Provide Rationale.
literature review of clinical outcomes. *Drugs, 78*, 463-478. https://doi.org/10.1007/s40265-018-0881-y	switching from a reference biologic to a biosimilar leads to altered clinical outcomes, enhanced immunogenicity, compromised safety, or decreased efficacy for patients.	evaluating supportive care and therapeutic agents. 14,225 unique individuals. Seven different molecular entities. 14 disease states.	Embase databases up to June 30, 2017, using terms biosimilar pharmaceuticals or biologic factors. End points reported in descriptive manner.	safety concerns or diminished efficacy is unchanged after switching from a reference biologic to a biosimilar medicine.	literature review of predominantly descriptive studies.	individual studies. Majority of studies descriptive in nature and not powered or designed to detect switch-related differences. Not possible to pool studies in a	supportive but not on its own merit. Could be combined with additional evidence to support switching.

Article Title, Author, etc. (Current APA Format)	**Study Purpose**	**Sample (Characteristics of the Sample: Demographics, etc.)**	**Methods**	**Study Results**	**Level of Evidence (Use Melnyk Framework)**	**Study Limitations**	**Would Use as Evidence to Support a Change? (Yes or No) Provide Rationale.**
						meta-analysis.	
Coory, M., & Thornton, K. (2019). Randomized clinical endpoint studies for trastuzumab biosimilars: A systematic review. *Breast Cancer Research and Treatment, 176,* 17-25. https://doi.org/10.1007/s10549-019-05227-7	To assess the evidential role of randomized clinical endpoint studies in the marketing approval of trastuzumab biosimilars.	Seven randomized clinical endpoint studies for five trastuzumab biosimilars	PubMed and ClinicalTrials.govsearch of randomized studies up to January 31, 2019 using the term trastuzumab biosimilar.	Using surrogate endpoints, each biosimilar was not different from Herceptin in any clinically important way.	Level 1: Systematic review of RCTs.	Studies not powered for safety endpoints. Small sample size (100 to 500 in each arm).	Yes. Best use of this review would be to adopt biosimilars into practice by assessing in vitro data as opposed to long-term clinical outcomes

Article Title, Author, etc. (Current APA Format)	Study Purpose	Sample (Characteristics of the Sample: Demographics, etc.)	Methods	Study Results	Level of Evidence (Use Melnyk Framework)	Study Limitations	Would Use as Evidence to Support a Change? (Yes or No) Provide Rationale.
							such as progression free survival or overall survival.
Hanes et al. (2017). A randomized, single-blind, single-dose study evaluating the pharmacokinetic equivalence of proposed biosimilar ABP 980 and trastuzumab in healthy male subjects. *Cancer Chemotherapy and Pharmacology, 79,* 881-888. https://doi.org/10.1007/s00280-017-3286-9	Compare the pharmacokinetic (PK) profiles of biosimilar ABP 980 and reference trastuzumab.	157 healthy males ≥ 18 years of age but ≤ 45 years of age.	Conducted in accordance with the Declaration of Helsinki and the ICH E6 Guidelines on Good Clinical Practice. Randomized, single-blind, single-dose, three-arm,	The study demonstrated similarity of ABP 980 to both EU and US trastuzumab. No differences in safety and tolerability	Level 2: RCT.	ANAs not centrally confirmed.	Yes. Establishes the biosimilarity of trastuzumab-anns. Supports use of the biosimilar in place of the reference

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			parallel-group study. Subjects randomized 1:1:1 to single infusion ABP90, trastuzumab (US) or trastuzumab (EU) PK parameters calculated using non-compartmental techniques (WinNonlin Professional Network	noted among treatments.			product in approved indications.

Article Title, Author, etc. (Current APA Format)	Study Purpose	Sample (Characteristics of the Sample: Demographics, etc.)	Methods	Study Results	Level of Evidence (Use Melnyk Framework)	Study Limitations	Would Use as Evidence to Support a Change? (Yes or No) Provide Rationale.
			Edition, Version 6.3). Safety analysis included descriptive summaries of AEs and incidence of ADAs.				
Jacobs et al. (2017). Biosimilars for the treatment of cancer: A systematic review of published evidence. *BioDrugs, 31,* 1-36. http://doi.org/10.1007/s40259-016-0207-0	To collate all published data to assess the weight of available evidence for proposed	36 publications involving 23 studies in oncology and chronic inflammatory diseases for bevacizuma	Search of Medline, Embase, ClinicalTrials.gov,National Library of Science and ISI Web of Science databases up to September 2015.	The proposed biosimilars exhibit close similarity to their originators.	Level 1: Systematic review of controlled studies.	At the time of analysis, limited outcomes data were available from published conference	Yes. Determining biosimilarity is not dependent on outcomes data but rather on

Article Title, Author, etc. (Current APA Format)	Study Purpose	Sample (Characteristics of the Sample: Demographics, etc.)	Methods	Study Results	Level of Evidence (Use Melnyk Framework)	Study Limitations	Would Use as Evidence to Support a Change? (Yes or No) Provide Rationale.
	monoclonal antibody biosimilars and intended copies for the treatment of cancer.	b, rituximab, and trastuzumab originators.	Search of conference proceedings from 2012 to July 2015.			s abstracts only. Molecules unable to be compared like for like.	proving degree of similarity. This review supports the use of the biosimilars studied.
Mengato et al. (2019). Trastuzumab biosimilar in metastatic breast cancer: Evaluating equivalence with originator using network meta-analysis. *International Journal of Clinical Pharmacology and Therapeutics*, *57*(3), 160-162.	To demonstrate that MYL-14010 biosimilar trastuzumab is as effective	8 RCT involving the use of trastuzumab MYL14010 and originator trastuzumab.	Medline and Pubmed search using words trastuzumab, Herceptin, and metastatic breast cancer.	MYL14010 biosimilar is as effective as its originator in terms of HR and PFS.	Level 1: Meta-analysis of RCTs.	Clinical trial information extracted only from ClinicalTrials.gov so some studies	Yes. Analysis supports the use of Mylan's biosimilar trastuzumab-dkst for any

Article Title, Author, etc. (Current APA Format)	Study Purpose	Sample (Characteristics of the Sample: Demographics, etc.)	Methods	Study Results	Level of Evidence (Use Melnyk Framework)	Study Limitations	Would Use as Evidence to Support a Change? (Yes or No) Provide Rationale.
https://doi.org/10.5414/CP203351	as its originators in terms of hazard ratio of PFS.	Pooled analysis with 1,955 patients.	Results filtered by article type (meta-analysis). Comparison of hazard ratio values for biosimilar and originator trastuzumab. CI 95%.			could have been missed. Only 17 conferences were searched and some proceeding could have been missed.	indication in which the reference product is indicated.
Minckwitz et al. (2018). Efficacy and safety of ABP980 compared with reference trastuzumab in women with HER2-positive early breast cancer (LILAC study): A	To compare the clinical safety and efficacy of ABP 980	725 women aged 18 years or older, had histologically	RCT, multicenter, double-blind, active-controlled equivalence trial.	ABP 980 and trastuzumab had similar safety outcomes in	Level 2: RCT.	Local and central labs did not agree on predefined	Yes. LILAC study supports use of

Article Title, Author, etc. (Current APA Format)	Study Purpose	Sample (Characteristics of the Sample: Demographics, etc.)	Methods	Study Results	Level of Evidence (Use Melnyk Framework)	Study Limitations	Would Use as Evidence to Support a Change? (Yes or No) Provide Rationale.
randomized, double-blind, phase 3 trial. *Lancet Oncology, 19*, 987-998. http://dx.doi.org/10.1016/s1470-2045(18)30241-9	with that of trastuzumab in women with HER2-positive early breast cancer.	confirmed HER2-positive invasive early breast cancer, an Eastern Cooperative Oncology Group performance status score of 0 or 1, and were planning to have surgical resection of the breast tumor with sentinel or	Patients assigned 1:1 to receive ABP 980 or trastuzumab with a permuted block design computer-generated randomization schedule. Co-primary efficacy endpoints risk difference and risk ratio of pathological complete response in breath tissue and	both the neoadjuvant and adjuvant phases of the study.		equivalence margins. Clinical response of breast cancer to neoadjuvant therapy not assessed.	biosimilar trastuzumab-anns where reference trastuzumab is indicated based on central confirmation of equivalence.

Article Title, Author, etc. (Current APA Format)	Study Purpose	Sample (Characteristics of the Sample: Demographics, etc.)	Methods	Study Results	Level of Evidence (Use Melnyk Framework)	Study Limitations	Would Use as Evidence to Support a Change? (Yes or No) Provide Rationale.
		axillary lymph node dissection and neoadjuvant chemotherapy.	axillary lymph nodes.				
Pegram et al. (2018). PF-05280014 (a trastuzumab biosimilar) plus paclitaxel compared with reference trastuzumab plus paclitaxel for HER2-positive metastatic breast cancer: A randomized double-blind study. *British Journal of Cancer, 120,* 172-182. https://doi.org/10.1038/s41416-018-0340-2	To compare PF-05280014 (biosimilar) with reference trastuzumab. Primary end point	707 females ages ≥ 18 years with HER2+ metastatic breast cancer with at least one measurable lesion by RECIST criteria.	1:1 randomization from 4/4/14 to 1/22/16 to IV PF-05280014 or trastuzumab-EU in standard dose. Randomization via automated interactive web-based response system.	When given as first-line therapy for HER2+ metastatic breast cancer, PF-05280014 demonstrated equivalence to reference	Level 2: RCT	Study did not assess current standard first-line treatment with dual HER2 blockade.	Yes. Evidence supports no clinically meaningful difference in PF-05280014 with paclitaxel

Article Title, Author, etc. (Current APA Format)	Study Purpose	Sample (Characteristics of the Sample: Demographics, etc.)	Methods	Study Results	Level of Evidence (Use Melnyk Framework)	Study Limitations	Would Use as Evidence to Support a Change? (Yes or No) Provide Rationale.
	RR for ORR.		Investigators blinded to treatment arms. Primary end point: ORR.	trastuzumab-EU in terms of ORR. No statistically significant differences in PFS, OS, or DOR were observed.			verses reference trastuzumab. Outcomes were equal among both groups. Study also supports confirmatory trials with dual blockade therapy. Biosimilar now approved

Article Title, Author, etc. (Current APA Format)	Study Purpose	Sample (Characteristics of the Sample: Demographics, etc.)	Methods	Study Results	Level of Evidence (Use Melnyk Framework)	Study Limitations	Would Use as Evidence to Support a Change? (Yes or No) Provide Rationale.
							in the US under the brand name Trazimera.
Reinmuth et al. (2019). PF-06439535 (a bevacizumab biosimilar) compared with reference bevacizumab (Avastin), both plus paclitaxel and carboplatin, as first-line treatment for advanced non-squamous non-small-cell lung cancer: A randomized, double-blind study. *BioDrugs*, *33*, 555-570. https://doi.org/10.1007/s40259-019-00363-4	To compare PF-06439535 (biosimilar) with reference bevacizumab, both with caboplatin and paclitaxel as first-line therapy for	719 adult patients ages ≥ 18 years with non-squamous, newly diagnosed stage IIIB or IV NSCLC or recurrent NSCLC. Patients required to	1:1 randomization to PF-06439535 plus paclitaxel and carboplatin or reference bevacizumab-EU plus paclitaxel and carboplatin. Randomized was computer-generated.	Among patients with advanced non-squamous, NSCLC, PF-06439535 demonstrated similarity to reference bevacizumab-EU in	Level 2: RCT	Majority of recruitment was from 10 countries outside the US.	Yes. Study does support the validity of biosimilarity but was conducted using EU-based products. Adds to the body

Article Title, Author, etc. (Current APA Format)	Study Purpose	Sample (Characteristics of the Sample: Demographics, etc.)	Methods	Study Results	Level of Evidence (Use Melnyk Framework)	Study Limitations	Would Use as Evidence to Support a Change? (Yes or No) Provide Rationale.
	advanced non-squamous NSCLC. Primary end point ORR.	have one measurable lesion by RECIST criteria.	Investigators blinded to arms. Randomized 5/21/15 to 11/14/16. Primary endpoint: ORR.	terms of efficacy. Safety profiles of both products were comparable.			of safety data for biosimilars and supports the use of US-biosimilar Avastin. PF-06439535 is now approved in the US under the brand name Zirabev.

Article Title, Author, etc. (Current APA Format)	**Study Purpose**	**Sample (Characteristics of the Sample: Demographics, etc.)**	**Methods**	**Study Results**	**Level of Evidence (Use Melnyk Framework)**	**Study Limitations**	**Would Use as Evidence to Support a Change? (Yes or No) Provide Rationale.**
Sharman et al. (2020). A randomized, double-blind, efficacy and safety study of PF-05280586 (a rituxan biosimilar) compared with Rituximab reference product (MabThera) in subjects with previously untreated CD20-positive, low-tumor-burden follicular lymphoma (LTB-FL). *BioDrugs, 34,* 171-181. https://doi.org/10.1007/s40259-019-00398-7	Compare PF-05280586 (biosimilar) with reference rituxmab in subjects with previously untreated CD20-positive, low-tumor-burden follicular lymphoma (LTB-FL).	394 adults ages ≥ 18 years with CD20+ LTB-FL without lymphoma-related B symptoms, ECOG PS 0-1	Web-based automated-response system used for 1:1 randomization to 375 mg/m2 of PF-05280586 or rituximab-EU once weekly for 4 weeks. Subjects stratified by FLIPI2 scores. Primary endpoint: efficacy and ORR. Secondary endpoints: PFS,	The safety, efficacy, immunogenicity, PK and PD were similar between both PF-05280586 and rituximab-EU up to 52 weeks. CR rates were similar.	Level 2: RCT	Does not show that biosimilar is equivalent in every indication for which rituximab is approved (this is not required by the FDA). Subjects received four doses as opposed to eight doses, the	Yes. PF-05280586 is now licensed in the US as Ruxience. Evidence supports that PF-05280586 is equivalent to reference rituximab without a compromise in

Article Title, Author, etc. (Current APA Format)	Study Purpose	Sample (Characteristics of the Sample: Demographics, etc.)	Methods	Study Results	Level of Evidence (Use Melnyk Framework)	Study Limitations	Would Use as Evidence to Support a Change? (Yes or No) Provide Rationale.
	Primary end point ORR.		CR at 26 weeks, TTF, DOR, OS, safety, and immune events.			standard of care. Interpretation of AE data may be limited by size of the study.	efficacy or safety when used instead of brand name rituximab.
Viswabandya et al. (2019). Randomized, double-blind, pharmacokinetic equivalence trial comparing DRL-rituximab with mabthera in patients with diffuse large b-cell lymphoma. *Journal of Global Oncology*, *5*, 1-13. https://doi.org/10.1200/JGO.19.00248	To compare the pharmacokinetics (PKs) of DRL-rituximab biosimilar and originator	151 patients with untreated DLBCL who were eligible to receive cyclophosphamide, doxorubicin,	Patients were randomly assigned at a one-to-one ratio to receive DRL_RI or RMP for six 21-day cycles of rituximab plus CHOP, with 18 months of follow-up after	Rates for B-cell depletion/repletion, immunogenicity, and adverse events were comparable in both groups.	Level 2: RCT.	Study conducted in single country.	No. Study does confirm biosimilarity but approval of this product has not

Article Title, Author, etc. (Current APA Format)	Study Purpose	Sample (Characteristics of the Sample: Demographics, etc.)	Methods	Study Results	Level of Evidence (Use Melnyk Framework)	Study Limitations	Would Use as Evidence to Support a Change? (Yes or No) Provide Rationale.
	rituximab mabthera.	vincristine, and prednisone (CHOP) therapy.	day 1, cycle 6 (C6). Primary end point was C1 PKs, measured as area under the plasma concentration-time curve from day 0 to 21 ($AUC_{0\text{-}21\ days}$) and maximum plasma concentration (C_{max}). Equivalence was defined as 90% CIs for the DRL_RI/RMP geometric mean ratios (GMRs) within 80% and 125%.	Both the biosimilar and reference rituximab have equivalent PKs.			cleared the FDA.

Article Title, Author, etc. (Current APA Format)	Study Purpose	Sample (Characteristics of the Sample: Demographics, etc.)	Methods	Study Results	Level of Evidence (Use Melnyk Framework)	Study Limitations	Would Use as Evidence to Support a Change? (Yes or No) Provide Rationale.
			Secondary end points included efficacy noninferiority measured by objective response rate (ORR) at C6 and event-free survival and overall survival at 87 weeks, PK equivalence at C6 and PD equivalence (rate of B-cell depletion and repletion), safety, and immunogenicity.				

Article Title, Author, etc. (Current APA Format)	Study Purpose	Sample (Characteristics of the Sample: Demographics, etc.)	Methods	Study Results	Level of Evidence (Use Melnyk Framework)	Study Limitations	Would Use as Evidence to Support a Change? (Yes or No) Provide Rationale.
Xavier et al. (2018). Phase III, randomized, double-blind study comparing the efficacy, safety, and immunogenicity of SB3 (trastuzumab biosimilar) and reference trastuzumab in patients treated with neoadjuvant therapy for human epidermal growth factor receptor 2- positive early breast cancer. *Journal of Clinical Oncology*, *36*(10), 968-974. https://doi.org/10.1200/JCO.2017.74.0126	To compare SB3 (biosimilar) with reference trastuzumab in patients treated with neoadjuvant therapy for human epidermal growth factor receptor 2-positive early	800 females ages 18 to 65 years. ECOG PS 0 to 1. Patients with confirmed primary invasive adenocarcinoma of the breast, HER2+.	Block stratified randomization 1:1 to receive either SB3 or EU-sourced tratuzumab IV every 3 weeks in the neoadjuvant setting for 8 cycles concurrently with standard dose chemotherapy. Primary endpoints: efficacy, safety, PK, immunogenicity.	Equivalence for efficacy was demonstrated between SB3 and trastuzumab on the basis of the ratio of bpCR rates. No clinically meaningful differences in terms of safety and immunogenicity	Level 2: RCT	Different product lots were used for the reference drug leaving room for drift which may or may not impact study results.	Yes. SB3 is now approved in the US under the name Ontruzant. This evidence supports the biosimilarity of Ontruzant to reference brand trastuzuma

Article Title, Author, etc. (Current APA Format)	Study Purpose	Sample (Characteristics of the Sample: Demographics, etc.)	Methods	Study Results	Level of Evidence (Use Melnyk Framework)	Study Limitations	Would Use as Evidence to Support a Change? (Yes or No) Provide Rationale.
	breast cancer. Primary end point			between the two products.			b and allows for the use of Ontruzuantwhere reference trazumab is indicated.
Yang et al. (2019). Efficacy and safety of anti-cancer biosimilars compared to reference biologics in oncology: A systematic review and meta-analysis of randomized controlled trials. *BioDrugs, 33,* 357-371.	To review the safety and efficacy data of available biosimilars in oncology.	23 RCTs. 8RCTs with biosimilar rituximab; 6 RCTs with biosimilar bevacizumab; 9 RCTs with biosimilar	Systematic review of RCTs located from search of PubMed, Embase, the Cochrane library, ClinicalTrials.gov, the ISI Web of Science, and	The existing evidence suggests highly comparable efficacy and safety profiles between monocolon	Level 1: Systematic review and meta-analysis.	Some studies did not include OS and PFS outcomes. Unable to assess publication bias due to	Yes. Evidence suggests a similar efficacy and safety profile for mono-clonal antibody

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		trastuzumab.	Chinese databases (CNKI, Wanfang, and SinoMed) from inception to December 31, 2018. Keywords included biosimilar and cancer. Review conducted according to PRISMA statement.	al antibody biosimilars and the reference biologics in oncological drugs.		< 10 studies for each outcome.	biosimilars relative to reference products.

Note. AEs=adverse effects. ANAs=antineutrophil antibodies. CI=confidence interval. G-CSF=granulocyte-colony stimulating factor. RCTs=randomized controlled trials.

Appendix B

IRB Approval Confirmation

Date: 5-29-2021

IRS#: IRB-FY20-21-913

Title: Feasibility of Biosimilar Integration in Oncology Practice

Creation Date: 5-13-2021

End Date:

Status: Approved

Principal Investigator: Kelley Mayden

Review Board: Research Ethics OfficeSponsor:

CITI PROGRAM

Completion Date 19-Mar-2021
Expiration Date 18-Mar-2024
Record ID 41697083

This is to certify that:

Kelley Mayden

Has completed the following CITI Program course:

Not valid for renewal of certification through CME.

CITI Good Clinical Practice
(Curriculum Group)
CITI Good Clinical Practice Course
(Course Learner Group)
1 - Basic Course
(Stage)

Under requirements set by:

Ballad Health System IRB

CITI
Collaborative Institutional Training Initiative

This GCP training contains all of the attested CITI Program modules from the **GCP for Clinical Trials with Investigational Drugs and Medical Devices (U.S. FDA Focus) Version 2**. This ICH E6 GCP Investigator Site Training meets the Minimum Criteria for ICH GCP Investigator Site Personnel Training identified by TransCelerate BioPharma as necessary to enable mutual recognition of GCP training among trial sponsors.

Verify at www.citiprogram.org/verify/?wa9684541-8a98-46f9-96b1-2ae9f53f34c7-41697083