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Introduction of Biosimilar Therapeutics Into Nephrology Practice in the United States: Report of a Scientific Workshop Sponsored by the National Kidney Foundation

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Biosimilars are biologic medicines highly similar to the reference product with no meaningful clinical differences in terms of safety, purity, and potency. All biologic medicines are produced by living cells, resulting in an inherent heterogeneity in their higher order structures and post-translational modifications. In 2010, the US Congress enacted legislation to streamline the approval process for biosimilars of products losing patent protection, with the goal of decreasing costs and improving patient access to therapeutically important but expensive biologic agents. In 2015, the US Food and Drug Administration approved the first biosimilar agent through this pathway. Approval of additional biosimilar agents in the United States, including those used by nephrologists, is anticipated. Given the relative lack of knowledge regarding biosimilars and their approval process and a lack of trust by the nephrology community regarding their safety and efficacy, the National Kidney Foundation conducted a symposium, *Introduction of Biosimilar Therapeutics Into Nephrology Practice in the U.S.*, September 17 to 18, 2015. Issues related to manufacturing, the regulatory approval process, interchangeability, substitution/switching, nomenclature, and clinician and patient awareness and acceptance were examined. This report summarizes the main discussions at the symposium, highlights several controversies, and makes recommendations related to public policy, professional and patient education, and research needs.

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INDEX WORDS: Biosimilar; biologic; erythropoietin analogue; dialysis; regulatory; therapeutic equivalency; reference agent; drug approval; safety; efficacy; cost; anemia; nephrology; end-stage renal disease (ESRD); pharmacovigilance; interchangeability.

B iologic products have been available for several decades as important therapeutic options for a number of serious conditions.¹ Biologics are substances produced by living cells using biotechnology (ie, recombinant DNA technology, controlled gene expression, or antibody technologies) and include a wide range of substances, such as recombinant hormones, growth factors, blood products, monoclonal antibody-based products, recombinant vaccines, and advanced technology products (eg, gene and cell therapy biological products).¹ Because biologics are produced by living cells, as opposed to chemical reactions that produce small-molecule drugs, biologics have an inherent heterogeneity in their higher order structures and post-translational modifications.

Biosimilars, as described by the US Food and Drug Administration (FDA), are biological medicines (biologics) that are “highly similar to the US-licensed biological product [also referred to as “reference” or “originator” product] notwithstanding minor differences in clinically inactive components...there are no clinically meaningful differences between the biologic product and the reference product in terms of the safety, purity, and potency of the product.”² It may be interesting to note that due to clinically insignificant structural heterogeneity secondary to multiple

manufacturing changes over time,³ many current reference biologics can be likened to “biosimilars” of the originally licensed product, although they are not designated so by the FDA.

Although the first biosimilar was approved and marketed in Europe in 2006, an abbreviated licensure pathway for biosimilars in the United States was enacted in 2010 as part of the Patient Protection and Affordable Care Act. It is anticipated that the availability of FDA-approved biosimilars in the United States will allow for reduced cost of and increased

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patient access to biologics.^{4,5} Nine of the 10 highest Medicare Part B expenditure drugs in 2014 were biologics, accounting for more than \$9 billion in Medicare Part B spending.⁶ There is growing awareness of the potential for impending biosimilar development and approval as drugs in several therapeutic categories are known to have expiring patents.⁷ It is unclear what the full economic effect of biosimilars in the United States will be, but the Congressional Budget Office has estimated a reduction in cumulative total spending on biologics of \$25 billion by 2018.⁸ More recently, the Rand Corporation estimated that biosimilars could result in a reduction of \$44.2 billion in spending (4% of all spending on biologics) between 2014 and 2024.⁹

Although some products considered biosimilar in other regulatory environments gained FDA approval before the new pathway was created, only 2 agents (filgrastim and infliximab) deemed to be a biosimilar according to the current regulatory pathway were approved by the FDA as of April 2016.¹⁰ Guidance from the FDA on biosimilars has been slow to emerge due to debates by stakeholders over how stringent the standards for new biosimilar approvals should be and whether approved biosimilars should be used interchangeably with reference products going forward.^{11,12} In 2015, the FDA released final guidance for industry on scientific¹³ and quality¹⁴ considerations and a draft guidance on nonproprietary naming of biologic products that also addressed interchangeability.¹⁵ Interchangeability refers to the ability of a pharmacist to substitute a biosimilar product for the reference product without intervention by the physician or advanced practice provider who prescribed the reference biologic product. The designation of “interchangeable” requires higher standards than “biosimilarity” alone and the sponsor must demonstrate that “if the biologic product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biologic product and the reference product is not greater than using the reference product without such alteration or switch.”¹⁵ The FDA has solicited input from stakeholders to guide its development of the final rule on these issues. A timeline of FDA guidance for the regulatory approval of biosimilars is shown in [Table 1](#).

Clinicians remain concerned about the safety, efficacy, and appropriate use of biosimilars. A 2013 survey of multiple clinical disciplines found there was a low level of understanding of the differences between biosimilars and generics, as well as the differences between biosimilars and reference biologics (>66% rated their understanding as “fair” or “poor”). Nearly 100% of respondents indicated a high level of

Table 1. Timeline of FDA Guidance for the Regulatory Approval of Biosimilars

Timing	Action
March 2010	Biologics Price Competition and Innovation Act passed as part of the Affordable Care Act
February 2012	Draft guidance on biosimilars: scientific considerations, quality considerations, questions and answers
March 2013	Draft guidance on formal meetings with FDA and sponsors
May 2014	Draft guidance on biosimilars: clinical pharmacology data
September 2014	FDA announces “Purple Book” (lists of licensed biologic products)
March 2015	First biosimilar approved
April 2015	Final guidance on biosimilars: scientific considerations, quality considerations, questions and answers
May 2015	Draft guidance on biosimilars: naming and interchangeability, additional questions and answers
March 2016	Draft guidance on labeling of biosimilar products

Abbreviation: FDA, US Food and Drug Administration.

need for continuing education on biosimilars.¹⁶ The oncology community published a position paper regarding regulatory and clinical considerations for biosimilar oncology drugs in 2014,¹⁷ many themes of which are reflected in this report.

BIOSIMILARS IN NEPHROLOGY

Optimizing the safety and efficacy of the treatment of anemia is one of the key challenges in chronic kidney disease (CKD) management.¹⁸ Anemia is increasingly prevalent as CKD progresses, affecting nearly 80% of patients with CKD stage 5.¹⁹ The many facets of anemia management in patients with CKD are superimposed against a climate of recent changes in anemia treatment. In Europe, several epoetin biosimilars have received marketing authorization, and data to date show that all these agents, considered by the European Medicines Agency to be therapeutically equivalent to the reference drugs,²⁰ have safety profiles that are also similar to the reference drugs.²¹ In the United States, all FDA-approved erythropoiesis-stimulating agents (ESAs) were erythropoietin analogues until 2012, when a synthetic pegylated peptide with no structural similarity to recombinant human erythropoietin (peginesatide [Omontys, Affymax]) was approved for use in patients undergoing dialysis. However, this drug is no longer available in the United States because of a voluntary manufacturer recall due to postmarketing reports of fatal anaphylactic reactions.^{22,23} It should be noted that the adverse reactions to peginesatide were not due to

immunogenicity, which is one of the major safety concerns regarding biosimilar agents. Nonetheless, the change in ESA formulation with peginesatide raised concerns among nephrologists regarding the potential for toxicity. At least 2 biosimilar erythropoietin analogues are in a later-stage approval pathway in the United States.^{24,25}

To date, literature on biosimilars has arisen primarily from European sources because of agents that are available to clinicians in these countries. Although the position paper summarized in **Box 1** specifies the need for informing European hematologists regarding biosimilars, it is clear that nephrologists in the United States are a key clinician group in need of education because of their regular use of biologics. Education on basic information to provide a context for biologics and nephrologist-specific information that applies to specific conditions, such as anemia, is a crucial step in ensuring informed and optimal care of patients with kidney disease.

One of the major concerns regarding biologics and biosimilars is immunogenicity. Because these products are all proteins, they have the potential of being recognized as foreign by the body and inducing an immune response. The immune response may manifest as the production of neutralizing antibodies that could decrease the efficacy of the therapeutic agent; as anaphylaxis or an immune complex disease with manifestations of serum sickness such as fever, arthritis, and vasculitis; or the cross-reacting of the antibody with the native hormone, leading to significant morbidity. In the case of ESAs, the development of antibodies that cross-react with native erythropoietin can lead to pure red cell aplasia (PRCA), a severe form of anemia due to the selective absence of red blood cell production by the bone marrow. The

epidemiology of PRCA is an excellent lesson regarding how fragile the process for the production, packaging, and distribution of biologic products can be. The first collection of PRCA cases occurred in Europe when the stabilizing agent in a reference ESA interacted with the rubber in the plunger of prefilled syringes.²⁶ Two cases of PRCA occurred when a biosimilar ESA in Europe interacted with the tungsten used to manufacture prefilled syringes.²⁷ Both these episodes occurred in the highly regulated European market, where the approval process for new medications is rigorous and systems for postapproval pharmacovigilance are well developed. In the first collection, the incidence of PRCA radically decreased with a manufacturing change and with a shift from subcutaneous to intravenous (IV) administration of the ESA.²⁸ In less well-regulated markets such as Thailand, PRCA occurred at a rate of 1 in 2,068 patients at risk due to the use of ESAs developed with poor oversight of manufacturing, packaging, and distribution processes for biologics.²⁹ These experiences have raised concerns among nephrologists regarding the risk for PRCA from biosimilar ESAs. It should be noted that none of the biosimilar ESAs approved and in use in Europe since 2007 has been associated with PRCA except for the small number of cases attributed to the tungsten interaction.²⁷ Due to concerns primarily regarding PRCA, the United Kingdom did not approve a biosimilar epoetin until 2014, which is 7 years after the rest of the European Union did so.

To address these regulatory and clinical concerns, the National Kidney Foundation (NKF) sponsored a scientific workshop on *Introduction of Biosimilar Therapeutics Into Nephrology Practice in the U.S.*, held September 17 to 18, 2015, in New York. The symposium's objectives were to examine issues related to manufacturing, the regulatory approval process, interchangeability, substitution/switching, nomenclature, and clinician and patient awareness and acceptance. The meeting, attended by 43 experts, was organized to allow an in-depth discussion on: (1) public policy, (2) education, and (3) research opportunities. This report summarizes the main discussions at the meeting, highlights several controversies, and makes recommendations related to the mentioned areas.

PUBLIC POLICY WORK GROUP REPORT

The Biologics Price Competition and Innovation (BPCI) Act of 2009 creates an abbreviated licensure pathway for biologic products shown to be biosimilar to or interchangeable with an FDA-licensed reference product. The intent of the BPCI Act was to make biologics more affordable by providing a clear pathway to approval that facilitates the insight that the

Box 1. Recommendations From Italian Hematology Societies Regarding Biosimilars

- To introduce biosimilars onto the market, transparent impartial information must be provided to prescribers and other health care providers
- Physicians in the subspecialty must be educated about the fundamental concepts and key issues related to biosimilars
- Because decisions concerning prescribing and substitutability are complicated and given that opinions are unlikely to be unanimous and can be expected to be vulnerable to conflicts of interest, professional societies should make it a priority to make appropriate information available
- To assist clinicians in making informed prescribing choices related to biosimilars, professional societies should organize scientific meetings and produce guidelines
- To help health care professionals make appropriate clinical decisions, scientific societies should have the goal of ensuring access to all data pertaining to biosimilars

Based on Barosi et al.⁴⁶

biosimilar product is similar to the reference product with regard to chemical structure, efficacy, safety, potency, pharmacokinetics, and pharmacodynamics. Approval can be granted by demonstrating “biosimilarity” of a new product to a previously approved and licensed reference product that has been shown to be safe and effective. The BPCI Act left open several implementation issues to be left to the discretion of the 2 responsible federal agencies: the FDA and the Centers for Medicare & Medicaid Services (CMS). The FDA has issued “guidance” on the approval process for biosimilar drugs^{2,5,8-10} (Table 1), and the CMS has addressed payment for biosimilars under Medicare Part B in regulations published on November 6, 2015.³⁰

Five policy issues were discussed and recommendations of the group follow.

How Should Biosimilars Be Named?

In August 2015, the FDA issued draft guidance on how they intended to name biosimilars.¹⁰ The goals of the naming convention were to help minimize inadvertent substitution and to facilitate pharmacovigilance. The FDA also desired to avoid inaccurate perceptions of the safety and effectiveness of biological products based on their licensure pathway. To accomplish these goals, the FDA proposed a name with 2 parts: a core name that would be the component shared among all related biological products, and a suffix that would be 4 lowercase letters that are unique and “devoid of meaning.” There was broad support for the core name, but there was discussion regarding the alternate use of a company identifier as the suffix. It was generally believed that inclusion of a company identifier as the suffix might make it easier for physicians and advanced practice providers to know which biosimilar they were prescribing. However, the recommendation of the FDA, as well as the need to rename should a company be acquired or change its name, made a non-company-specific suffix devoid of meaning the preferred option. A secondary nomenclature issue is whether interchangeable biosimilars should have the same suffix as the innovator drug. The work group strongly thought that doing that would violate the second FDA goal of promoting pharmacovigilance.

What Should Be the Policy of Individual States Regarding Substitution/Switching of Interchangeable Biosimilars?

Currently there is universal substitution for generic pharmaceuticals unless a physician or licensed nonphysician advanced practice provider writes “Dispense as written” (DAW; or words to that effect). When there are multiple suppliers of a generic drug, each time a pharmacist fills a prescription, she or he

may do so with a generic produced by a different manufacturer from the originator product. These decisions are made regularly without notification of the prescribing provider. Should interchangeable biosimilars be managed in the same manner? This policy falls under state pharmacy dispensing laws. Nineteen states and Puerto Rico have passed legislation to permit automatic substitution of interchangeable biosimilars by the pharmacist. Virginia and Oregon have provisions obligating physician (or provider) communication, but these provisions expire in 2015 and 2016, respectively. As of 2016, whether providers are informed is moot because there are no interchangeable biosimilars. Work group members generally believed that physicians and advanced practice providers should be notified in a timely manner of the substitution and that prescribers should continue to have the ability to prohibit substitution by a DAW designation. There was concern by the work group that although a product may be interchangeable in its pharmacologic effect, the active ingredient may be made using a different biological system and may be associated with unintended effects that cause concern. Individual patients might also have idiosyncratic reactions to the inactive components of a biosimilar, precluding its use in their case. When a product has an established safety record over at least 5 years, physicians and advanced practice providers may not need to be regularly informed of switches. A derivative issue is whether patients should be informed of a substitution or switch. The work group believes that any process of substitution or switching should be fully transparent and therefore the patient should be informed at the time of dispensing whether he or she is receiving the reference product or an interchangeable or biosimilar one. A similar level of transparency should be provided by health insurance plans, hospitals, infusion centers, and dialysis care providers. As noted in the previous section, it should always be possible to identify the specific biosimilar dispensed in case the patient develops an unexpected reaction to the agent.

How Should Biosimilars Be Coded for Payment and Pharmacovigilance Purposes?

The CMS proposes that all biosimilars of a particular reference biologic drug be given the same billing code and the same payment. It is anticipated that the payment would be derived from 100% of the weighted average selling price of the biosimilar(s) plus 6% of the average selling price of the reference drug. The first part of the proposal, that all biosimilars related to a particular reference product have the same Healthcare Common Procedure Coding System (HCPCS), raised the concern that such a policy would weaken pharmacovigilance. The work group

endorsed the principle that whatever coding system is used by the CMS strengthen and not weaken pharmacovigilance. There are several alternative methodologies that would allow the CMS and private payers to implement the CMS pricing policy and still use the claims process to track individual biosimilars. An in-depth analysis of these potential payment approaches to allow optimal pharmacovigilance was beyond the scope of the symposium and most of the participants' expertise. However, it was noted that there is an existing field on currently used claims forms for subcodes or modifiers of National Drug Codes. The Medicare Payment Advisory Commission (MedPAC) in comments to the CMS proposed rule for payment of biosimilars under Medicare Part B stated that the proposal would foster price competition and reduce government expenditures.³¹ The Congressional Budget Office earlier reached the same conclusion.³² While the work group supported the principle of lower prices to the health care system in general, as well as lower beneficiary prices (as a result of lower coinsurance), it did not want to compromise pharmacovigilance for incremental cost savings.

What If Any Postmarketing Surveillance Studies Should Be Required?

On March 6, 2015, the FDA approved filgrastim-sndz (Zarxio Injection, Sandoz) as a biosimilar to filgrastim (US-licensed Neupogen, Amgen). The FDA required no postmarketing studies. The work group believed that biosimilars should require postmarketing surveillance. The specific studies should be based on the safety profile of the reference product. The work group generally agreed that the initial period of postmarketing surveillance period should be in the range of 2 to 4 years, as adopted in Europe.

Should There Be Uniform Guidance for Health Plans Regarding Payment Tiers?

The work group strongly believed that health plans should be free to operate independently with respect to payment for biosimilars.

EDUCATION OF PHYSICIANS AND DIRECT PATIENT CARE PROVIDERS WORK GROUP REPORT

Physicians and advanced practice providers who prescribe biosimilar agents should be offered education to define and clarify the differences between small-molecule and generic products, large-molecule biologic reference drugs, and biosimilars. When prescribers entertain the option of prescribing a biosimilar ESA, they must understand that a batch of either epoetin alfa or darbepoetin alfa does not constitute an absolutely homogeneous group of molecules due to the inherent heterogeneity of products produced by living cells, compounded by

manufacturing changes that occur over time. Only the primary structure of the molecules is replicated exactly, whereas the overall structure is not. **Box 2** outlines the important educational concepts regarding biosimilar agents. Because biosimilar products will not be made by the manufacturer of the reference product, the quality of the newer product may be questioned. The track record of quality for each manufacturer of biosimilar agents, in addition to cost, will be of particular importance for decision makers who determine which products are available on their formulary. These complex molecules can be challenging to produce, so clinicians need information about the manufacturing process and any problems encountered by the manufacturer, especially because such issues have occurred in the past. With respect to ESAs, biosimilars must acknowledge the possibility of PRCA, just as the reference drugs do. When feasible, risks should be quantitatively expressed. For each biosimilar product, the dose and dosing strategies must be illustrated in comparison to the reference molecule. Comparative data regarding efficacy should be reported. All potential severe adverse effects should be made available to prescribers, even if they are the same as the reference molecule. Any adverse effects significantly different or more severe than those associated with the reference molecule should point to a manufacturer-related "defect" and thus underscores the importance of postmarketing surveillance.

Educational programs for patients will be important. Although several features of this program would be similar to the program for physicians and advanced practice providers (ie, definition of a biosimilar, efficacy, and safety), additional considerations are required (**Box 3**). If a clinician chooses to switch a patient from a reference molecule product to a biosimilar, the reason for that switch should be made clear to the patient. As with all patient education programs, the patient's ability to understand, process, and recall complex medical information must be considered, and educational tools should be created for different levels of medical literacy.³³⁻³⁵ This is particularly important for patients with end-stage renal disease, who often have impaired cognitive function, multisystem disease, and complex medical and dialysis prescriptions. There is some evidence

Box 2. Important Educational Concepts Regarding Biosimilar Agents

- Concept of reference vs biosimilar molecule
- Efficacy
- Safety
- Manufacturing process equivalency
- Adverse serious event frequency
- Agent-specific serious adverse effects

Box 3. Educational Issues for Patients Regarding Biosimilar Agents

- Are there any specific advantages or disadvantages of biosimilar agents when compared to the reference agent?
- Are the known potential risks the same for the biosimilar product as for the reference product?
- Are there any possible additional risks?
- How much clinical experience has there been for a biosimilar compared to the reference molecule product?
- How will the cost of the product figure into the decision for the reference vs biosimilar product?

that engaging peers as mentors and teachers may assist patients in managing their disease.³⁶ Such engagement is particularly important because patients with CKD have low health literacy in general.³⁷

**BIOSIMILARS RESEARCH IN KIDNEY DISEASE
WORK GROUP REPORT**

An important goal of complementary studies of biosimilars in kidney disease is to examine the unmet needs that might not be addressed by the trials or other vetting for regulatory approval. Data need to be collected and analyzed for a number of pertinent study questions, including overcoming clinician and patient uncertainty about the safety and efficacy of biosimilars and their interchangeability with the reference products. A fundamental question is how to examine the interchangeability in the context of a regulatory construct as opposed to distinct clinical implications that might extend beyond regulatory requirements. A relevant analogy is the use of different iron dextran formulas in the United States under the same generic designation. Beginning in 2008, the same Medicare billing code has been used for different types of iron dextran, an injectable iron product used for treatment of iron depletion. The perceived interchangeability across 2 distinct molecular weights of iron dextran, namely lower (INFeD, Watson Pharma, Inc) versus higher (Dexferrum, American Regent) molecular-weight formulations, was questioned as a result of different safety and adverse-event profiles reported in observational studies conducted after those needed for FDA approval of these agents.³⁸ This historical example demonstrates the importance of research to identify pre- and postmarketing commonalities and distinctions of individual agents that may (or may not) eventually be considered interchangeable under a unifying biosimilar designation.

Clinically relevant differences should be examined for individual medication lots that may use the same international nonproprietary name or identical suffix provision. To that end, data integrity is of high importance in the postapproval phase of biosimilars to enable research on multiple drug comparisons. Among potential factors that may inflate the

differences across so-called interchangeable agents is the frequency of changes in biosimilar molecules over a given period in a given patient population. Studies are needed to examine putative risk factors that may contribute to distinctions based on differential effects at the individual patient level and among different populations, for example, by age, sex, race, ethnicity, comorbid conditions, CKD stage, and end-stage renal disease duration. Another clinically relevant target for immediate research is to examine effective approaches to optimize surveillance for and detection of PRCA, which could be difficult to identify given typical cases with multiple exposures of different ESAs. It should be noted that the cluster of PRCA cases in Europe related to the interaction between the stabilizing agent in the ESA and rubber in the pre-filled syringes was not identified rapidly by pharmacovigilance and was primarily driven by the insights of Dr Nicole Casadevall and her colleagues.²⁶ To ensure high-quality and reproducible research, well-thought-out standard operating procedures should be designed and in place. These standard operating procedures are essential for effective workup and comprehensive data collection for the targeted studies. Some of the examples of the needed steps and tests may include, but are not limited to, measuring reticulocytes and relevant antibodies and other serologic tests.

Given that there may appear to be little incentive for pharmaceutical companies to pursue postapproval trials of biosimilars, the dialysis industry should be engaged proactively in discussions related to additional research on biosimilars. Concerted efforts are needed to collect safety data from dialysis providers and enhance the effectiveness of the postapproval research in order to ensure the external validity of the studies. Both large and small dialysis organizations should be approached. Collaboration with large dialysis companies is of particular importance given that about two-thirds of all maintenance dialysis patients in the United States are currently under the care of 2 large dialysis organizations, Fresenius Medical Care and DaVita Healthcare Partners. Legitimate motivations and potential risks and liabilities for the dialysis organizations need to be effectively and comprehensively explored and transparently addressed in order to encourage the dialysis providers to allow and enhance design and conduct of these studies. As an example, the “tracking and tracing” approaches can be automated in the dialysis clinics and incorporated in the standard operating procedures that can be realigned with the dialysis treatment protocols and procedures. The route of administration is an exceptionally relevant piece of information that needs to be captured with high levels of granularity and accuracy. Whereas there seems to be little worry about IV

administration of the biosimilar agents for anemia management in CKD, a higher level of surveillance is expected for subcutaneous administration of biosimilar ESAs given the historical background (higher rates of PRCA with subcutaneous injections).³⁹ In addition to major adverse events, non-life-threatening symptoms that are relevant to patients and providers should be collected with greater detail.

Pragmatic trials with cluster randomization or retrospective cohort trials can be designed with the support of dialysis providers, similar to studies that have been conducted to compare IV paricalcitol and doxercalciferol administrations or IV versus oral vitamin D analogues.⁴⁰ Studies in healthy volunteers have indicated that erythropoietin therapy has effects on platelet reactivity,^{41,42} but the clinical significance in patients with CKD is unclear.⁴³

In addition to surveillance data collection and postmarketing registry research, research could examine outcomes such as those listed in [Box 4](#).

The mentioned proposed lines of research can also serve to address the safety questions related to the use of biosimilars in not only in-center hemodialysis

patients, but also in home dialysis and non-dialysis-dependent patients with CKD, who are more likely to receive subcutaneous injections of these agents. To that end, national Medicare and Veterans Administration databases can be examined, in which such granular data can be better tracked for complementary research given that trials that are performed for FDA approval might not have captured certain levels of potential adverse events or rare patient symptoms in the “needle-in-a-haystack” areas. More thought and consensus building meetings and discussions may be needed pertaining to efficacy metrics, dose response, transfusion indications, packaging for low versus high doses, billing code (J-code), and nature of adverse reactions that may not be required by the FDA but that can be clinically relevant to both patients and physicians. Potential measures for efficacy research include but are not limited to those listed in [Box 4](#).

It may be argued that who benefits economically versus clinically from the use of biosimilars may not be a scientific research question; however, careful investigation of the financial aspects of biosimilars in the context of safety and efficacy research can expand the scope of relevant study questions considerably. It is far from clear whether the lower costs of biosimilar ESAs would prompt a newer look at relatively costly iron products and how such emerging scenarios can effectively be studied. Dialysis providers may choose to use a biosimilar ESA and direct the savings to enhance patient care and support research for patient benefit. In addition, broader level benefits may be examined, for instance, whether society at large and taxpayers value a slower rate of increase in health care costs as a result of biosimilar use.

In conclusion, reliable individual agent identification is essential for effective surveillance and related postapproval research on biosimilars. Expanded pharmacovigilance beyond the FDA-mandated levels is needed to ensure that investigators can more effectively develop and choose from among high-priority research questions for the safety and efficacy of biosimilars. Additional adverse events in addition to traditionally known conditions such as PRCA, including anaphylaxis, should be examined. Although it is highly unlikely that biosimilar ESAs will show a difference from originator ESAs due to the preapproval vetting that requires the former to be highly similar to the latter with no clinically meaningful differences in safety, purity, and potency, postmarketing research may explore areas such as thromboembolic events, platelet markers, hypertension research, dose-response phenomenon, iron indexes, hard outcomes, and patient-reported outcomes using larger patient cohorts and longer durations of exposure that exceed the statistical power of phase 3

Box 4. Potential Areas for Outcomes Research With Biosimilar Erythropoiesis-Stimulating Agents

- “Hard” outcome measures
 - Mortality
 - Hospitalizations
 - Chronic kidney disease progression rate
 - Renal transplant survival
- Intermediate outcome measures
 - Thromboembolic events, including cerebrovascular and cardiac events
 - Dialysis vascular access events, including occlusion and patency longevity
 - Endothelial function tests
 - Platelet indexes, including platelet counts, mean platelet volume, platelet function tests, and other biomarkers such as p-selectin
 - Blood pressure-related data, including peak and nadir blood pressure values and changes in antihypertensive medications
 - Carcinogenicity data
- Efficacy data
 - Frequency of blood transfusion
 - Administered iron supplementations, including repletion (“load and hold”) vs maintenance therapy
 - Hemoglobin levels and other indexes of iron and anemia
 - Prescribed dose of the drug
- Patient-reported outcome measures
 - Health-related quality of life
 - Clarity of the information conveyed and accuracy of the perception of patients about switching between reference agents and biosimilars
 - Patients’ opinions, thoughts, and beliefs pertaining to the use of biosimilars, including the views of vulnerable patients with regard to potentially hidden therapy switches and putative subterfuge

studies. Finally, cost-effectiveness analyses in the real world will be welcome to demonstrate that biosimilar products have achieved their goal of reducing health care expenditures while increasing patient access to valuable therapeutic agents.

SUMMARY

In developing and finalizing its guidance for approval of biosimilar agents, the FDA has drawn upon its experience in evaluating the results of manufacturing process changes by the sponsors of reference biologics that may result in small physicochemical or bioactivity changes in the product, its experience in evaluating biosimilar products that have been in the registration pipeline since the pathway was legislated by Congress in 2010, and the extensive European experience with biosimilar evaluation, approval, and pharmacovigilance since 2007. Congress legislated the approval pathway for biosimilars to bring these lower cost products to market in a timely and efficient manner to decrease overall health care costs and increase patient access while protecting patient safety. As of the end of 2015, only one agent, filgrastim-sndz, a granulocyte colony-stimulating factor, had been approved via this pathway in the United States. In April 2016, the FDA approved infliximab-dyyb (Inflectra, Pfizer), a biosimilar of infliximab (Remicade, Janssen). The approval of Hospira/Pfizer's biosimilar epoetin was anticipated in November 2015, but the application was returned to the sponsor by the FDA with a request for additional information. The uptake of biosimilar ESAs in Europe has varied among countries and relates mostly to the price differential between the biosimilar agents and the reference agents. Overall, biosimilar ESAs had about one-third of market share for all ESAs in Europe as of 2014.⁴⁴

When biosimilar ESAs are approved in the United States, decisions regarding their use will be a function of cost savings versus residual safety concerns. In the environment of end-stage renal disease, because biosimilar ESAs will be included in the bundled payment, cost savings will initially accrue to the dialysis provider but will likely be eventually reclaimed by the CMS in another round of rebasing the bundled payment.⁴⁵ It is likely that health plans and dialysis providers will encourage the use of biosimilar ESAs by requiring less hassle and paperwork to prescribe them versus the reference agent, so interchangeability becomes less of a driver to the use of biosimilar agents than formulary decisions. If a biosimilar ESA is deemed interchangeable, the process for substitution at the pharmacy level will vary according to state law, but all states will allow the prescriber to prevent substitution by writing "DAW" or words to that effect. If substitution occurs, it will be vital for both the

prescriber and patient to be informed so that any adverse reactions can be attributed to a specific agent. Pharmacovigilance to identify patterns and trends of adverse events will require unique identifiers for each agent.

Biosimilars are a new frontier of therapy in the United States and constitute a learning, research, and public policy opportunity for all stakeholders. Despite the current global use of biosimilars, there remains a lack of data. The expansion of biosimilar ESAs into the US market should answer many questions regarding their efficacy, safety, and pharmacoeconomics at a level of statistical power not previously achieved. In order for this occur, the appropriate educational, investigative, and policy (at the state and federal level) infrastructure must be in place as these agents are approved. As a principal stakeholder and patient advocate, the nephrology profession will be looked to for leadership in this process.

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