AMERICAN COLLEGE OF RHEUMATOLOGY
POSITION STATEMENT

SUBJECT:	Biosimilars
PRESENTED BY:	Committee on Rheumatologic Care
FOR DISTRIBUTION TO:	Members of the American College of Rheumatology Medical Societies Members of Congress Health Care Organizations/Third Party Carriers Managed Care Entities

POSITION:

The ACR strongly believes that safe and effective treatments should be available to patients at the lowest possible cost. Decisions regarding the approval and use of biosimilars must be driven by sound science and consider several observations and guiding principles, including:

1. The size, complexity, and heterogeneity of biologics (and thus biosimilars) necessitate a greater degree of scrutiny in their analytical evaluation than what is required for small molecule generics.

2. In addition to adequate pharmacokinetic and pharmacodynamics studies, clinical data are necessary to ensure the safety and efficacy of biosimilars, and to provide the necessary level of confidence for their use by patients and clinicians. Furthermore, the collection of long-term post-marketing data for each individual biosimilar is necessary to monitor for less common but nevertheless important adverse events.

3. Post-marketing surveillance studies are needed in children as well as adults, as toxicities and long-term sequelae may be different in these disparate populations. The Best Pharmaceuticals for Children Act (BPCA), which reauthorizes the pediatric studies provision of FDA Modernization and Accountability Act to improve safety and efficacy of pharmaceuticals for children, should apply to biosimilars.

4. FDA labels (package inserts) should clearly indicate whether a biosimilar is interchangeable with the reference (originator) biologic. FDA labels should also clearly delineate all indications for which a biosimilar is approved and specify whether the supporting clinical data for the indication are derived from studies of the biosimilar or the reference biopharmaceutical.

5. When starting new biologic therapy, clinicians consider a variety of patient-specific factors which include severity of illness, the most appropriate route of administration and mechanism of action. Should the appropriate medication chosen have a biosimilar option, the ACR supports initial biosimilar use. However, if the most appropriate biologic does not have a biosimilar option, it should be approved by the patient's insurer, and not be switched to a different biologic class.

6. In patients on established therapy, the final decision to switch from a reference product to a biosimilar should rest with the prescriber and the patient. The ACR opposes insurer-mandated forced switching to biosimilars and is concerned over frequent non-medical switching with biosimilars. In jurisdictions where substitution by someone other than the prescribing provider is lawful, the prescribing provider and the patient should be notified immediately when a substitution is made.

BACKGROUND:

Biologics are complex molecules produced by living cells using recombinant DNA technology. Biologics have an important role in many areas of medicine, particularly in rheumatology. Due to the nature of their complexity, biologics are costly. These high-costs are concerning for the financial sustainability for the healthcare system and our patients. Biosimilars, also called follow-on biologics, are "highly similar" to the reference product, also known as originator, and may offer some cost-savings. The ACR agrees with the need for more cost-effective biologic therapeutics and believes that biosimilars offer hope of cost reduction if physicians and patients can be sufficiently reassured of their efficacy and safety through rigorous scientific study of these products [1].

Biologics are extraordinarily complex molecules. There are three main categories of biologics that are currently available for treatment of people with rheumatic disease: (1) products that are almost identical to natural products the body makes, which are often used as replacement therapy or to augment the body's own response; (2) monoclonal antibodies that bind to soluble or cell surface proteins and block pathways or cells; and (3) engineered proteins that mimic receptors (soluble receptors or receptor antagonists), but are soluble and designed to be stable in humans.

Biologics are created by incorporating DNA sequences into living cells and utilizing the genetic transcription, protein translation, and processing machinery of the specific cell line to produce an engineered protein product. Once the biologic protein is produced in the living cell, an extensive purification process is required to isolate the desired protein. Biologics used in rheumatic diseases are typically large (1000-fold larger than aspirin) monoclonal antibodies (a type of protein) with complex three-dimensional structures. This structure determines their function but also gives rise to the risk of adverse events that they may cause. The structure is determined not only by the original DNA sequence but also by multiple post translational modifications which

can vary significantly based on the details of the manufacturing process [2]. Companies that produce biosimilars use the reference biologic to reverse engineer the biosimilar product and do not have access to proprietary manufacturing procedures of the original biologic. Therefore, the biosimilar is not expected to be identical to the innovator product.

It is imperative that physicians and patients feel confident in the safety and efficacy of approved drugs. The ACR commends the Food and Drug Administration (FDA) in its commitment to stringent regulation of processes required to approve biosimilars. In the US, the Biologics Price Competition and Innovation (BPCI) Act of 2009 established an abbreviated approval pathway for biologics demonstrated to be biosimilar to an FDA licensed biological product, known as 351(k). Currently a product can be considered biosimilar to a reference product if, based on data derived from analytical studies, animal studies, and a clinical study or studies, the product is shown to be 'highly similar' to the reference product, notwithstanding minor differences in clinically inactive components, and if there are no clinically meaningful differences in terms of safety, purity and potency.

In addition, a biosimilar product may be deemed 'interchangeable' if it meets certain higher standards. According to the FDA, an “interchangeable” biological product is biosimilar to the reference product and can be expected to produce the same clinical result as the reference product in any given patient. If administered more than once to an individual (as many biological products are), the risk in terms of safety or diminished efficacy of alternating or switching between the biologic product and the reference product will not be greater than the risk of using the reference product without such alternation or switch [4]. Once determined “interchangeable” two biological products may be substituted for each other (i.e., interchanged) by a pharmacist as specified by state statutes without intervention from the prescriber. Pharmacists will be responsible for knowing which biological products are interchangeable and which will require a new prescription from the prescribing clinician before dispensing.

The ACR recognizes increasing cost pressures may cause payers to push patients towards biosimilars. Payers should provide transparent guardrails around “non-medical switching” that allow the patient and prescriber to choose the best treatment for that patient with tenuous disease control.

In jurisdictions where substitution of interchangeable biosimilars by pharmacists is allowed, the prescriber and the patient should be notified immediately when a substitution is made. This is especially important in light of the short dosing interval of some biologics (as few as three days) which increases the number of doses a patient can receive and thus the risk of adverse reactions attributable to the new drug even within a short time frame after it is dispensed.

Because some populations of patients with rheumatic diseases may be more susceptible to adverse drug reactions and disease states in some organ systems respond differently to one biologic compared to another, extrapolation should be pursued with caution and only when

deemed appropriate by the prescriber in the best interests of the patient. Extrapolation should not be allowed in response to policies conceived by payers to substitute use a biosimilar in place of a reference drug in a stable patient for the sole purpose of cost savings. Specifically, it is inappropriate for a payer to insist upon the use of a biosimilar for an indication for which it has not specifically received FDA approval.

Given the tremendous number of factors that influence the potential safety and efficacy of biosimilars, FDA labels (package inserts) must be unambiguous and delineate differences between biosimilars and reference products. FDA labels should clearly delineate all indications for which the biosimilar is approved, for which indications it is interchangeable with the reference biologic (if any), and specify whether the supporting clinical data for each indication are derived from studies of the biosimilar or the reference biopharmaceutical.

Efficacy and safety of therapeutics in adults does not guarantee safety and efficacy in children. For this reason, the Best Pharmaceuticals for Children Act (BPCA), which reauthorizes the pediatric studies provision of FDA Modernization and Accountability Act to improve safety and efficacy of pharmaceuticals for children, should apply to biosimilars. Understanding the unique considerations of pediatric patients, care must be taken to ensure that children are on an appropriate treatment path. If it is determined that the most appropriate medication for a pediatric patient is a reference (originator) biologic rather than a biosimilar, it should be approved by the patient's insurer and not be switched to a different biologic. The ACR also supports continued comparative effectiveness research efforts to better define the role of biologics and biosimilars in the treatment of diverse populations of adult and pediatric patients [5].

In summary, the ACR supports the use of cost-effective medications as deemed appropriate by the treating physician or prescriber who takes into account multiple considerations specific to individual patients. If a biologic medication is prescribed that does not have a biosimilar available, the medication should be approved and not changed to a different biologic class. In patients already on establishing biologic therapy, insurers should not mandate switching to a different biosimilar medication and the prescribing clinician as well as the patient should be notified of any substitution.

REFERENCES:

1. Bridges SL, White DW, Worthing AB, Gravallese EM, O'Dell JR, Nola K, et al, on behalf of the American College of Rheumatology. The science behind biosimilars: entering a new era of biologic therapy. Arthritis Rheumatol 2018;70:334-44.

2. Hmiel LK, Brorson KA, Boyne MT. 2015. Post-translational structural modifications of immunoglobulin G and their effect on biological activity. Anal Bioanal Chem 407:79.
3. Calvo B and Zuñiga L. 2012. The US approach to biosimilars: The long-awaited FDA approval pathway. Biodrugs 26:357.
4. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandAp proved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm241718. htm. Retrieved April 24, 2016.
5. Comparative Effectiveness Research, a Position Statement from the American College of Rheumatology, available at http://www.rheumatology.org/Practice-Quality/Administrative-Support/Position-Statements