

Good afternoon. My name is Gregory Schimizzi and I am a practicing rheumatologist in Wilmington, North Carolina representing the Coalition of State Rheumatology Organizations. Ours is a national entity composed of 26 state and regional member societies representing private practicing rheumatologists in the US. We endeavor to promote excellence in care and access to care for patients with autoimmune diseases.

Rheumatologists are keenly aware of the dramatic, long-term, life changing improvements in thousands of Americans with autoimmune diseases since the introduction of biologic agents. These agents have provided significant impact on patients' quality of life by preventing disability, decreasing morbidity, and lowering mortality where other conventional agents have failed. These medications are expensive and rheumatologists support the development of less expensive alternatives as long as they are proven to be safe, well tolerated and preferably have fewer and certainly no more side effects than the innovator products. It is our opinion that the approval pathway for follow-on biologics must include: clinical trials for all products, should foreclose the ability for interchangeable products at this time, and prohibit automatic retail substitution by assigning a unique non-proprietary name. I will focus on these key issues: biosimilarity, interchangeability, and pharmaco-vigilance regarding patient safety.

### **Biosimilarity**

Biologics are protein molecules produced by very complex manufacturing processes involving genetic engineering and are products of mammalian, bacterial or other living cell cultures. By virtue of their targets, origins and protein nature, these agents affect immune function, can themselves be immunogenic and require the highest level of purity and consistency. This is in stark contrast to other generic drugs. Other generics are produced by organic chemistry processes and are required to comply with FDA reviewed efficacy and safety standards before marketing. But the complexity of biologics and their potential for other effects demand that new standards be developed to address this unique group of products.

A responsible regulatory process needs to consider the structural as well as functional features of the new agent with particular emphasis on differences relative to reference innovator compounds already available. It is not enough for follow-on agents to have similar effectiveness targeting an in-vivo cytokine, receptor, or cell surface marker molecule. Considering the meaning of “biosimilar” and “approval under an abbreviated pathway”, it is important to emphasize that minor differences in primary amino acid sequence can cause significant alterations in a protein molecule’s secondary and tertiary structures resulting in a “biosimilar” protein with vastly different effects. The effects on the targeted cytokine, receptor, surface marker protein or other substances, and the potential for immune stimulation may vary considerably including differences in affinity /avidity profile, differential propensity for adverse reactions and even pharmacodynamic properties all resulting from amino acid substitutions in key locations.

#### **Interchangeability**

*Practicing rheumatologists believe that there is not sufficient scientific understanding of potential “biosimilars” to allow for an interchangeability of biological products. While we hope that advances in scientific knowledge will provide such standards in the future, they simply do not exist at this time. Therefore, in the interest of our patients, relying on biological products, I urge the FDA to foreclose this avenue until the science advances in this area. Anything short of barring interchangeability at this time would be detrimental to patient safety and would erode physician confidence in prescribing these medications.*

#### **Patient safety and Pharmacovigilance**

Patient safety must be paramount in considerations regarding approval of follow-on biologic agents. Adequate and appropriate FDA pre-approval evaluation as well as post-marketing surveillance must be included.

*Clinical trials to ensure that a follow-on biologic is safe, effective and free of different immunologic consequences not associated with the parent compound are necessary to provide physicians and patients with confidence*

*in these new agents. There simply is no substitute for testing these products given their degree of complexity and their effects.*

A good example of one such occurrence is the pure red blood cell aplasia that was linked to an erythropoietin follow-on agent after it was used in over 90 countries. One case of aplasia occurred in every 5,000 patients exposed. A great deal of investigation was required before the cause was ultimately defined. In rheumatology practices, we have seen a variety of positive responses and adverse reactions to different TNF alpha blockers. Adverse effects vary among different patients with the same disease who are given the same TNF blocking agent or in a single patient who receives different anti-TNF agents.

All adverse reactions are not always identified at the time of approval of these agents. A 2008 report published in JAMA found that 41 of 174 biologics approved since 1995 were the subject of 82 regulatory actions regarding safety. In this study, the probability of a first safety-related regulatory action was 14% 3 years after approval and 29% 10 years after approval.

***The FDA should provide a unique nonproprietary name for each biological product.*** This is the only certain way to track post marketing differences in monitoring adverse effects. Furthermore, the physician should always be involved in decisions regarding selection of the specific biologic agent being dispensed to his or her patient. Automatic retail substitution of biologics is not appropriate.

A unique non-proprietary name ensures that the patient receives the prescribed product, enhances traceability in the event of adverse post marketing experience, prevents inadvertent substitution and contributes to a reduction in medical errors. Nonproprietary names are the primary means for patients and practitioners to correctly identify products. Patients often do not retain product packaging that may contain other identifying information, such as lot numbers or manufacturers. Without the ability to distinguish the product **by name**, most patients will resort to referencing the class of product or the most widely advertised product. This will hinder efforts to identify the source of a

new problem, accurately associate patient experience with a specific product and will thwart the development of a meaningful safety profile for each medication.

Follow-on biologic labeling must provide accurate, specific and comprehensive information about the actual product, not the reference product. The physician and patient should be able to easily see (1) data on the actual product (which is contrary to the EU practice), and (2) the indications for which the product is approved and those for which it has not been approved. In order to facilitate informed decision-making, clear information must be readily available to the physician and patient.

In summary, we support the development of follow-on biologics as this will improve access to care for patients with serious rheumatologic illnesses as long as the pathway for approval assures the safety and efficacy of these agents and their immunologic effects are studied. Clinical trials are paramount since desired and adverse effects of follow-on agents may differ from the parent innovator compound. Once again for patient safety reasons, we urge the FDA to foreclose the ability for interchangeability at this and to maintain transparency for matching what is prescribed and what is dispensed. When examining potential risks regarding interchangeability, FDA must not only require specific clinical studies examining those substitutions within human subjects, but also needs to require additional post-marketing surveillance to monitor for new potential risks. Finally, the FDA should insist on a unique non-proprietary name for each biological product.

I offer my sincere thanks to the FDA for having this public hearing to discuss key issues of relevance to rheumatologists, other physicians, patients and other stakeholders.

**Thank you.**