Stakeholders Nov. 2 provided input to the Food and Drug Administration for its creation of an abbreviated pathway for biosimilars or follow-on biologics, with pharmacies expressing concern that new patient barriers will be imposed for these drugs, patient and physician groups advocating clinical trials and no automatic pharmacy substitution, and biopharmaceutical companies urging caution.

The two-day public hearing, which continues Nov. 3, was designed to obtain input on specific issues and challenges associated with implementing the Biologics Price Competition and Innovation Act of 2009. The measure, which is part of the Patient Protection and Affordable Care Act, provides for an abbreviated approval pathway for biological products that are demonstrated to be “highly similar” to, or “interchangeable” with, an FDA-licensed biological product.

Speaker after speaker acknowledged that the key challenge is that a biosimilar is similar but not identical to the original or reference biological product.

Marcia Boyle, president and founder of the Immune Deficiency Foundation, noted that immunoglobulin therapy for those with immune deficiency is complex and that the products used to treat these patients do not have specific amino acid sequences. Even slight changes in the manufacturing process can cause illness in patients, Boyle said, noting that 28 percent of patients reported serious side effects when they tried a new product for the first time and 13 percent when they switched product.

"Given these numbers, you can understand IDF’s concerns about an abbreviated pathway for approval for biosimilars,” Boyle said.

According to Boyle, the IDF recommended that FDA not waive clinical trials for biosimilars and that it rely on these trials. It also recommended that FDA exclude immunoglobulin products from its biosimilar pathway and that it institute strong post-approval surveillance. Finally, the IDF asked FDA to prohibit automatic substitution of biosimilars.

Patients, Physicians Want Trials
Janet Wyatt, representing the Arthritis Foundation, said, "Patients with inflammatory arthritis need to be assured that biologic and biosimilar therapies will be of high quality, accessible, safe and effective."

She said the foundation urges FDA to move expeditiously to create a regulatory pathway that provides appropriate oversight, ensures patient safety, and ensures access to these potentially lower-cost biologic products; require clinical studies to ensure biosimilars work as well as approved products in the targeted population; mandate rigorous post-marketing surveillance for any newly approved biologic and/or biosimilar and seek ways to improve the current system for reporting and responding to adverse events; and reach out to patient organizations, such as the Arthritis Foundation, to improve its communication efforts regarding biologic products.

Among the patient advocacy organizations, Seth Ginsberg, co-founder of the Global Healthy Living Foundation, characterized the proposed path to approval for biosimilars “as the vehicle for making money by disregarding the standards and practices that have created the biologics miracle.”

Not Generics
Describing biosimilars “as a step backward for science, for physicians, and for patients,” Ginsberg, who was diagnosed with spondyloarthropathy when he was 13, assured the panel that his organization’s members would welcome biosimilars, provided they are subject to the same rigorous testing, clinical trials, and post-marketing studies required of biologic drugs.

"Biosimilars, as they are currently proposed, represent another opportunity for health insurers to practice good economics by not allowing physicians to practice great medicine,” Ginsberg said. "Our members are already subject to health insurers' bottom-line-oriented policies that override doctors' judgment by requiring a patient to fail first on a medicine preferred by a health insurer before that patient is allowed to succeed on the prescribed medicine. Biosimilars would extend this practice.”

Ginsberg continued, “Even if it looks like the reference biologic, a biosimilar may not act like the reference biologic and, as the scientists say, ‘determinations of comparability' cannot be made for products that are not comparable. This is why we need clinical trial experience. We cannot extrapolate indications across biosimilars. Biosimilars cannot be considered as interchangeable with the biologics they attempt to copy. They are not identical, generic versions of biologics. That’s why nobody calls them generics.”
There must be post-marketing clinical and safety studies to find a way for patients, physicians, and government agencies to clearly differentiate between biosimilars and the original biologics and to track the molecules to their origin by manufacturer and batch, Ginsberg said. “We do it with eggs,” he said, referring to the recent situation of tainted eggs coming out of Iowa. “We must do it with biosimilars.”

Dr. Gregory Schimizzi, representing the Coalition of State Rheumatology Organizations, echoed patient groups' concerns. “Clinical trials are paramount,” he said. “There is no substitute for testing these products given their complexity. Also automatic retail substitution for follow-on biologics is not appropriate.”

Schimizzi urged the FDA to “close the avenue for interchangeability at this time.”

**Issue of Interchangeability**

Shein-Chung Chow of the Duke University School of Medicine's Department of Biostatistics and Bioinformatics discussed study design. He said crossed design, in which subjects are randomized to one treatment and later switched to another, is the design choice for bioequivalence, and parallel design, in which subjects are randomized to receive separate treatment, is a suitable design for biosimilarity. He suggested that the best approach would be a two-stage process of studies with crossover and parallel designs.

As for evaluating interchangeability, he said a higher order of crossover design would necessarily be employed and that bridging studies using biomarker data should be considered.

Laszlo Endrenyi of the University of Toronto's Department of Pharmacology said crossover studies would be ineffective and unethical and that parallel studies would not provide sufficient information on interchangeability.

“With follow-on biologics, biosimilars do not generally reflect therapeutic comparability. Therefore switching and alternating biosimilars should be pursued only with substantial caution,” he argued.

**Pharmacy Benefits Company's Views**

Scott Reid, CVS/Caremark's senior vice president of specialty pharmacy operations, voiced concern that no barriers that could inhibit patient access be imposed on pharmacies “working at the front lines,” and asked the agency to ensure that pharmacovigilance programs for biosimilar and interchangeable products be consistent with programs for the original products.

Reid also urged FDA to work with the Centers for Medicare & Medicaid Services (which covers certain biologics) to establish a regulatory process that not only allows for interchangeability of biologics but also aligns reimbursement incentives for payers, patients, and providers to choose a biosimilar.

Steve Russek, representing Medco Health Solutions and the Accredo Health Group, said that patient safety is of paramount importance. He also stated that the ultimate goal should be to ensure that as many biosimilars as possible are established as interchangeable.

Russek suggested that biosimilars of the same class be grouped under the same billing code and, once biosimilar products were established as interchangeable, they should have the same generic name so as not to confuse the patient or physicians.

He addressed the issue of the 12 to 13.5 years exclusivity established by the legislation and said that FDA should be very conservative about allowing that period to be extended.

**Branded, Generic Drug Companies**

Jim Shehan, vice president of corporate and legal affairs for Novo Nordisk Inc., a global health care company with a focus on diabetes care, said that FDA should proceed cautiously in exercising the interchangeability provision of the legislation. He said that all biosimilars should have unique names and that the product's labeling should clearly state that it is a biosimilar and whether it is deemed interchangeable.

F. Owen Fields of Pfizer Inc., a global pharmaceutical company, said, “From a practical perspective, interchangeability would need to be established for each reference product indication and subpopulation. An interchangeability standard may need to rest on compositional and functional sameness.”

Rivka Riven-Kreitman, vice president of global innovative R&D for Teva North America, a generic pharmaceutical company, advocated a balanced approach. While the complex nature of biologics warrants caution, conducting unnecessary clinical trials raises ethical questions and could make the products too expensive for patients to afford.
“Interchangeability should be allowed once biosimilarity has been established on a chemical and clinical level following a development program that includes a robust pivotal trial,” Riven-Kreitman said.

Dr. Sumant Ramachandra, senior vice president and chief scientific officer for Hospira Inc., a global specialty pharmaceutical and medication delivery company, discussed the company's experience in Europe for approval of its erythropoietin biosimilar and said that the standards it was asked to meet were higher than those for the reference product.

He recommended that use of a European Medicines Agency-approved reference product in pivotal biosimilar clinical trials should be permitted in bridging data to U.S.-licensed reference products. Ramachandra said that extrapolation of clinical data from one indication to other indications should be allowed with proper scientific justification and that the same pharmacovigilance system should be used for the originator biologic and biosimilar products.

Finally, Ramachandra recommended that FDA approach interchangeability on a case-by-case basis and should reflect how the product will be used in medical practice.

“Interchangeability is the ideal,” he said, “but it will not always be possible or necessary.”