FDA Issues Guidelines for Biosimilar Drugs

In the United States, the race to produce competitive copies of biologic drugs such as monoclonal antibodies has officially kicked off.

On February 9, the U.S. Food and Drug Administration (FDA) released draft guidelines for approval of biosimilar drugs, defined as products that are “highly similar to an already approved biological product, notwithstanding minor differences in clinically inactive components, and for which there are no clinically meaningful differences [from] the approved biological product in terms of the safety, purity, and potency.”

“These draft documents are designed to help industry develop biosimilar versions of currently approved biological products, which can enhance competition and may lead to better patient access and lower cost to consumers,” says Janet Woodcock, MD, director of FDA’s Center for Drug Evaluation and Research.

The 2010 Patient Protection and Affordable Care Act directed the FDA to work out approval mechanisms for biologics. Effective in 2014, original biologic reference products will receive 12 years of market exclusivity after their FDA approval.

FDA 351(k) applications for biosimilars “must contain, among other things, information demonstrating that the biological product is biosimilar to a reference product based upon data derived from analytical studies, animal studies, and a clinical study or studies, unless the FDA determines, in its discretion, that certain studies are unnecessary,” the guidelines say.

U.S. law gives a period of exclusivity for the first product that is not only biosimilar but interchangeable with the reference product. The bar of FDA approval is higher, considering such questions as whether health care providers or their patients would need instruction to make the switch. “At this time, it would be difficult as a scientific matter for a prospective biosimilar applicant to establish interchangeability in an original 351(k) application,” the guidelines note.

While the U.S. market for biosimilars is expected to become the largest by 2020, according to an analysis by IMS Health in Danbury, CT, such agents are already being sold in Europe, India, and other countries.

Pharmaceutical and biotechnology companies worldwide are gearing up for these opportunities. Manufacturers of original products are teaming up with firms that offer expertise in generic products. For instance, Amgen of Thousand Oaks, CA, signed an agreement in December with Watson Pharmaceuticals of Parsippany, NJ, to commercialize oncology biosimilars worldwide.

Development of a biosimilar requires significant technical capability and clinical trial expertise and may cost between $20 and $100 million exclusive of manufacturing plant expenses, says the IMS report.

In the United States, “stringent clinical requirements and an involved, potentially drawn-out procedure for resolving patent disputes are likely to delay the speed of uptake in the near future,” the report adds. “Behind every product patent there are several potential lines of defense for originator companies, including process patents.”

Cornering Cancer Cells

Individual cancer cells can be tricky to pin down for imaging. But now scientists have created a material coating that could trap them like Velcro (RSC Advances, published online February 1, 2012). The material positions macromolecules and cells for transmission electron microscopy (TEM), so scientists can peer down at their intricate molecular features.
“It’s hard to make these kinds of observations when molecules and cells are moving around,” says lead investigator Deborah Kelly, PhD, an assistant professor at the Virginia Tech Carilion Research Institute in Roanoke. “By holding things in place we can watch for early events of drug therapy.”

Conventional TEM, Kelly explains, generates images by firing electrons through dry tissues in a vacuum. But unlike live samples in a liquid environment, dry cells have distorted, deformed proteins.

Kelly’s collaborators at Protochips, Inc., in Raleigh, NC, got around the problem by flowing cells in solution through a nanofluidic chip maintained under the conditions needed for TEM. Applied within that device, the new coating—an affinity biofilm—can be labeled with adaptors that bind to cell surface receptors or to macromolecules of interest.

According to Kelly, the technology promises new opportunities for using TEM imaging to monitor the early stages of drug delivery. With nanometer resolution, TEM traverses the boundary between cellular and molecular imaging, revealing cell surface structures with unprecedented detail.

“We’d like to use this technology to watch how drugs penetrate into cancer cells,” Kelly says. “The advantage is that we can isolate specific cell populations that aren’t contaminated with other types of cells that we’re not as concerned with.”

Pancreas Cells Move Out Before Tumors Form

Researchers at the University of Pennsylvania have discovered one explanation for why pancreatic cancer usually remains undetected until after it has metastasized: At least in mice, the cancer cells start spreading even before they form primary tumors. The investigators also found that inflammation helps drive that process by encouraging the transformation of epithelial cells into mesenchymal cells that can enter the bloodstream (Cell 2012;148:349–61).

The change in color of these tagged mouse pancreas cells shows the epithelial-to-mesenchymal transition (EMT). The orange cells on the left have retained expression of cytokeratin-19. Cells that have undergone EMT on the right no longer express this epithelial marker and appear green.

Led by Ben Stanger, MD, PhD, a developmental biologist and assistant professor of medicine, the researchers bred mice with mutations in Kras and p53, genes often mutated in human pancreatic cancers. They also introduced an allele that tagged pancreatic epithelial cells with a green marker, allowing them to see how the cells developed and changed over time.

After about 1 to 2 months, the mice began to develop premalignant lesions, which progressed to pancreatic cancer after 4 to 5 months. But even before actual tumors formed, the pancreatic epithelial cells began adopting characteristics of mesenchymal cells and traveled to other sites, including the liver.

Hypothesizing that inflammation spurred the epithelial-to-mesenchymal transition (EMT), the scientists blocked inflammation by treating the mice with the immunosuppressant dexamethasone when the animals were 8 to 10 weeks old. The green cells undergoing EMT disappeared. Conversely, when the researchers induced pancreatitis with an agent that kills pancreatic duct cells, the number of green cells undergoing EMT increased.

The researchers also looked for these cells outside of the pancreas and found them seeding the liver and circulating in the blood of mice at 8 to 10 weeks of age, long before they would form actual tumors at the primary site. That discovery lends credence to the theory that inflammation may enhance metastasis by giving cells increased access to the bloodstream, says Stanger.

In an international phase III clinical trial, median length of survival for patients with metastatic colorectal cancer who were treated with Bayer’s multikinase drug regorafenib increased from 5 months to 6.5 months, a statistically significant jump. This could be the first new therapy in recent years to result in improvement for such patients.