IN brief

Variant predicts HCV response

A single DNA variant in the human genome can identify who will respond to hepatitis C virus (HCV) treatment and clear the virus. HCV is notoriously difficult to treat (*Nat. Biotechnol.* **27**, 305–306, 2009). Individuals with HCV infection are given weekly injections of polyethylene glycol–conjugated interferon α-2a—Pegasys, from Roche of Basel, or Peg-Intron, from Schering-Plough in Kenilworth, New Jersey—plus daily oral ribavirin. But the 48-week-long therapy is poorly tolerated, and not always successful: only 40–50% of infected individuals clear the virus. Now a study by Dongliang Ge at Duke University in Durham, North Carolina suggests it may be possible to tailor antiviral courses to the most appropriate patients. The Duke researchers analyzed 1,137 infected individuals from multi-ethnic backgrounds and their response to treatment in a genome-wide association study (*Nature* **461**, 399–401, 2009). They identified a group of single-nucleotide polymorphisms (SNPs) associated with treatment response in the region of the IL28B gene, which encodes an interferon-λ involved in viral suppression. About 80% of those individuals carrying two copies of an advantageous SNP cleared the virus during treatment. "It's a striking finding," says Raymond Chung, a hepatologist at Boston's Massachusetts General Hospital. Chung believes additional prospective studies could turn this SNP into a "useful clinical tool" if combined with other variables. Schering-Plough, who owns rights to Ge's SNP, is looking to develop a genetic test based on this marker. *Mike May*

First-to-market loses grip

The period of marketing exclusivity enjoyed by a first-in-class drug in the US has fallen dramatically. A report released by the Tufts Center for the Study of Drug Development (TCSDD) shows, among other things, the time between FDA approval of a first-in-class drug and a second drug dropped from 10.2 years in the 1970s to 2.5 years in 2000–2003. The study also shows that 87% of follow-ons in the 1990s were already in clinical trials by the time the breakthrough drug was cleared, and that secondary products were often approved with a priority rating. This all points to a shorter period of market dominance by the pioneering drug. First-to-market means less and less these days, says TCSDD director Kenneth Kaitin, who adds that "if you've got a superior product, it doesn't make any difference whether you're first or eighth." For firms looking to enter a market with a second-in-line product, that means evaluating the product for safety and efficacy and superiority before forging ahead. Daniel Ruppar, industry manager for pharmaceuticals and biotechnology in North America with Frost & Sullivan, of Mountain View, California, says that it's not necessarily preferable to have a second-in-class drug now, but admits that "the second drug can gain key learnings from the first," and "what really matters is which is the better drug." *Bob Carlson*

costs but, because the originator companies also drop their prices, market share may not shift so dramatically," she explains. The continuing fragmentation of the healthcare market in Europe makes it difficult to assess the overall market share changes accurately. However, Islah Ahmed, the global medical director of Hospira, located in Lake Forest, Illinois, has aggregated data for Germany, the biggest single national pharmaceutical market in Europe. The data show that two years after launch, biosimilar EPOs represent ~35% of unit sales of short-acting EPOs, whereas substitution rates for small-molecule generics can exceed 90% in the first year.

The second reason to think that a biosimilars pathway in the US will have a muted impact is that industry lobbies, such as Biotechnology Industry Organization in Washington, DC, and the Pharmaceutical Research and Manufacturers of America, also in DC, have been hard at work 'protecting their members' interests'. Several pieces of competing legislation came before Congress this year. Bills proposed by Senator Sherrod Brown (D-Ohio) and Representative Henry Waxman (D-CA), which gave the greatest encouragement to manufacturers of follow-on biologics by proposing a period of five or seven years respectively, have faded from view. In June, the US Federal Trade Commission argued for zero years' market exclusivity based on the premise that competition between originator compounds and biosimilars was likely to resemble brand-to-brand competition rather than a generic substitution model (*Nat. Biotechnol.* **27**, 677, 2009). The Obama Administration's position is that seven years of market exclusivity for novel biologic products is sufficient, in line with the interest of biosimilar producers.

Since July, however, the impetus has shifted to two 'pro-innovation' bills that have progressed through Congress rapidly because they are tied into the heath reform package (HR 3200). The Senate Health, Education, Labor and Pensions Committee introduced the 'Hatch Amendment' and the House Energy and Commerce Committee added the 'Eshoo Amendment'. Both propose to provide developers of pioneer products with 12 years' market exclusivity, regardless of the patent status of the product, based on an economic model outlined by Henry Grabowski of the Fuqua School of Business at Duke University (*Nat. Rev. Drug Discov.* **7**, 479–488, 2008).

Buoyed by such high-level support for biosimilar-friendly legislation, the public relations campaign is likely take a new and more aggressive twist. Colleagues of Bill Haddad recently undertook an *ad hoc* survey of drug bills at municipal, volunteer and not-for-profits hospitals—those hospitals which act as the safety net for the majority of American sick and uninsured. Haddad claims that the high prices for biologics affects those hospitals severely. "The 5% of patients treated with biologics account for 45% of the drug bills in those hospitals," he says. "Every Congressional district has hospitals that are struggling because of the high cost of biologics and that makes for a lot of local media coverage." The next phase in the campaign will involve a detailed cost-and-profit breakdown for current 'innovator' products.

Although the short-term political fireworks will establish the magnitude of the contribution that biosimilars can make in the US, the deliberations at WHO will likely shape the nature of the regulatory process that FDA ultimately implements. The WHO draft guidelines on similar biotherapeutic products (http://www.who.int/biologicals/publications/trs/areas/biological_therapeutics/BS2110Dft_guidelines_Final_HK_IK_29July_09.pdf) were closed for comments on October 9, 2009, and the document was being deliberated by the WHO Expert Committee on Biological Standards as *Nature Biotechnology* went to press.

The WHO document is a guideline and has no legal force on WHO member states. But the document has political significance because it is unlikely that it would contain proposals unacceptable to regulators in such countries as the United States and China. "Personally, we do not expect the USA to have a scientifically different approach to the EU or Japan," says Kox. "There are some significant principles in the [WHO] Guidelines." Jacques Mascaro, senior vice president, global regulatory affairs, pharmacovigilance and quality from Dublin-based Elan, was involved in establishing the EMEA biosimilar guidelines in the EU and has reviewed the WHO guidance documents as an innovator industry representative. He agrees that the WHO guidelines are "an important step" that provides "an agenda to move things along."

Mascaro was keen not to appear to be telling the FDA what to do. He nevertheless raised three key issues of interest. "Firstly, will the FDA take a case-by-case approach? Secondly, will it integrate the data and experience that already exists from assessments in the EU and elsewhere? And, thirdly, what will be the position with respect to the interchangeability of products?"

The WHO draft guidance provides clear direction to the first and third questions. It states that the basis for licensing a biosimilar—similar biotherapeutic product (SBP), in WHO parlance—depends on "its demonstrated similarity to a suitable reference biotherapeutic product in quality, nonclinical and clinical parameters." So, yes, there should be a case-by-case approach. Furthermore, the WHO guidance indicates that "automatic substitution of SBP is not recommended" and that decisions on interchange-

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