At a Pfizer's Analyst Day in March, Kindler said, "there will always be a competitive advantage in the space that will be a little different than small molecules."

Cowen analyst Cacciatore agrees. From an investor perspective, the capabilities to produce biogenerics are largely in big-cap pharma and big biotech, he says, even more so than in generics firms. "From a Wall Street perspective, people are thinking that it's the generic companies that are going to do it," he says. But Cacciatore counters that the formulation capabilities, manufacturing and sales force needed for follow-ons won't be interchangeable with small molecules. "You're going to need regulatory skills, the capital structure to take this on, and if you look at the [capital structures] of the generics companies, they just can't take this on, including a Teva."

That said, there's a large difference between follow-on biologics that fall into the 'me-too' category, like Dynepo and Omnitrope, and the so-called 'me-betters', which include the potential offerings from Teva-Cogenesys in which human serum albumin is hooked up to a biologic of interest. In this respect, Teva could be seen more as a specialty pharma company than a generics maker.

Stephen Kaldor, president and CEO of the biotech firm Ambrx, in La Jolla, California, notes that for follow-on biologics, "there's a primary interest in market differentiation," which by definition favors products in the me-better rather than me-too category. Me-betters—including Ambrx's mid-clinical-stage ARX-201, a growth hormone product that would offer less frequent dosing—may offer a longer half-life, an improved manufacturing process or more favorable dosing regimen.

"We've chosen to focus only on the me-better side, and partly that's market driven," Kaldor says. "People are starting to look more seriously, from a life cycle management and other perspectives, at true biosimilars. But I'd say the marketplace for a small biotech fits more with the me-betters." Development and commercialization of ARX-201, for example, is being shared with Merck Serono, in Geneva, which also sells a traditional growth hormone Saizen. The collaboration is an attractive amalgamation for life cycle management of the growth hormone franchise. History seems to back the approach. Indiana-based Eli Lilly moved from bovine to human insulin, Basel-based Roche shifted from recombinant interferon-α to the longer-lasting peglyated version (Pegasys), and Thousand Oaks, California–based Amgen's evolution of granulocyte colony-stimulating factor from Neupogen (filgrastim) to Neulasta (darbepoetin alfa) to Aranesp (darbepoetin alfa).

In the US, there's expectation that legislation around biogenerics could reach the President's desk this year. "It's inconceivable to me that it won't," says Cacciatore. Rawson is more sanguine about those prospects, and by extension, the likely commercial implications. "We would argue that even with a follow-on pathway, any biosimilars that would be approved would not be a near-term commercial option," Rawson opines.

The FDA will need time to develop regulations, and ongoing resource constraints will probably delay the introduction of a biogenerics regulation. Rawson points out that the FDA is still trying to absorb the last user fee act, the FDA Amendments Act (FDAAA, *Nat. Biotechnol.* **25**, 1061, 2007). "Some of the implementation deadlines for FDAAA are also being delayed," she says. FDA has a lot on its plate already, and to ask it to implement another high-profile piece of legislation any time soon "is probably asking a lot." The key commercial implication is that therapeutic substitution under a biogenerics pathway is a long way off. That means that uptake of products will be "a lot slower than what we've seen with small molecules," she concludes. And if there's no action on follow-on biologics next year, it could conceivably wait until 2012, when a bill could be attached to the fifth reauthorization of the prescription drug user fees act, PDUFA.

Large-cap pharma can sit back and see how the legislative pathway evolves, says Cacciatore. In the meantime, R&D continues apace. Shire's product for Gaucher disease, the gene-activated human glucocerebrocidase (GA-GCB), is in several phase 3 trials, two of which are expected to be completed in the spring of 2009. The GA-GCB should hit the market at a 30% discount to a competitive product from Genzyme. Shire's other products derived from Transkaryotic Therapies, which likewise target much less crowded markets than Dynepo, are also doing better. Sales of Elaprase (idursulfase) for Hunter syndrome hit $78 million in the third quarter of 2008, and Replagal (agalsidase alfa) for Fabry disease hit $44 million for the period.

There was disappointing news for Genzyme on the follow-on biologic front, last month. The FDA decided to delay a decision on whether the company could market a scaled-up version of its drug Myozyne (alglucosidase), already approved for Pompe disease. The Cambridge, Massachusetts–based biotech had to conduct a clinical study to establish the clinical effectiveness of the biological product's new scaled-up version made at its larger 2,000 liter plant. Genzyme expects the FDA's decision by February and European approval in the first half of 2009.

Mark Ratner *Cambridge, Massachusetts*

IN brief

Country-of-origin labels

A bill requiring drug labels to specify the country of manufacture for every ingredient has been introduced to the US Senate. The heparin contamination in March 2008 that led to 81 deaths raised concerns about the contents of foreign-made drugs coming into the US. In response to this and other crises involving imported drugs, Senator Sherrod Brown (D-Ohio) has proposed the Transparency in Drug Labeling Act as an amendment to the Federal Food, Drug and Cosmetic Act. The country-of-origin requirement would apply not only to active ingredients but to excipients too. At the same time, the FDA has announced that it will open its first overseas office this year. The office, in Beijing, staffed by eight US nationals and five Chinese locals, will provide technical advice, conduct additional inspections and form liaisons with government agencies and the private sector to develop certification programs for food and drug exports. Additional offices are planned in Shanghai and Guangzhou, as well as in India, Central America and parts of Europe. The Government Accountability Office (GAO) is concerned, however, that most FDA foreign inspections have focused on manufacturing plants named in new drug applications rather than follow risk-based assessments as is done in the US. In selecting foreign inspection sites, "the [FDA needs] to take the same factors into consideration and apply them in the same ways," says Marcia Crosse, GAO director of healthcare. *—Susan Kim*

Giants wrestle over ImClone

The struggle to gain control over ImClone and its cancer medication Erbitux (cetuximab) has ended with Eli Lilly the victor. The Indianapolis-based company outbid its pharma rival Bristol-Myers Squibb (BMS), announcing in October that it would acquire ImClone of New York for $6.5 billion in cash. At $70 per share, the deal represents a 51% premium to the closing price one day before the BMS bid became public. New York–based BMS started the bidding in July with a $4.5 billion offer for the 83% of ImClone it did not already own. But after upping its bid to $62, BMS decided it would not increase its offer. Sales of Erbitux, a chimeric anti-epithelial growth factor (EGFR) monoclonal antibody (mAb), are still growing. The drug is currently labeled for use in metastatic colorectal cancer and advanced head and neck squamous cell carcinoma. Investment bank Cowen & Co. of New York forecasts that Erbitux will bring in global revenue of $2.2 billion in 2009 with its second-generation fully-human mAb IMC-11F8 bumping sales to $3 billion by 2013. BMS might have wanted to gain rights to IMC-11F8, the promising successor to Erbitux currently mid-stage in the clinical trial process, which has potential to ultimately supersede Erbitux in the marketplace. "Bristol was price sensitive, but I'm not so sure I agree with that decision," says senior biotech analyst Eric Schmidt of Cowen. "My guess is that 10 years from now, Lilly's going to look very smart." *—George S Mack*