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Overdue process

Healthcare agencies were blindsided last month by a decision to suspend operations at the UK manufacturing facility of Chiron Corporation, the world's second largest producer of influenza vaccine. They shouldn't have been. Deviations from good manufacturing standards at the Liverpool plant had been documented two months earlier, and similar problems were detected in June 2003. Even more egg was on faces as a result of Chiron's assurance that bacterial contamination would only affect 6–8 million doses. It has turned out that none of the company's 2004 batch of vaccine is safe to use, with the result that the US has lost almost half of the 100 million doses it expected to have for this year's flu season. The depleted number of vaccine companies still doing business means that no company is in a position to step in and respond to the shortage.

Apart from prompting such questions as how one company with a facility in a foreign country could hold sway over the US supply of flu vaccine, the fiasco brings into sharp focus the lamentable state of the world's vaccine industry. Faced with the prospect of retooling aging vaccine plants in response to new regulations and a steady erosion in profit margins due to government bulk-buying, many companies simply have exited the sector. But one person's exit may be another's entrance, and advances in expression systems—the subject of several articles in this issue—though yet to impact the antiquated process of manufacturing influenza vaccines, one day will, concomitantly lowering at least some manufacturing costs.

A much closer horizon, however, is represented by recombinant generics. Considering that ~60 different approved protein drugs are currently produced in recombinant form, and the patent expirations of even some second-generation drugs are not far off, the 'find a hole and fill it' principle seems to be quite applicable. Add to this the political plum of driving down drug prices, and the continued delay of the US Food and Drug Administration (FDA) in issuing its guidance on generics becomes even more irritating. For once, European regulators have moved faster, but predictably the situation is only marginally less muddy; the European Medicines Agency's comparability guideline falls short of providing an abbreviated process, requiring instead that follow-on biologics complete a new filing and perform clinical trials on a case-by-case basis. This is a far cry from the abbreviated approval process for small-molecule generics.

To be fair to the regulators, protein drugs are indeed 'idiosyncratic' and, in contrast to chemically synthesized small molecule drugs, are derived from highly variable living sources (*e.g.*, mammalian cells or microorganisms). Most are formulated as complex mixtures that cannot be easily assayed or characterized. Changes in modifications, such as glycosylation, often influence stability, reaction kinetics, solubility, serum half life, *in vivo* activity and receptor binding. Therefore, regulators are correctly concerned with the problem of determining the types of test required to demonstrate that a brand protein and its generic copy are comparable in terms of protein purity, sequence, structure, species specificity, pharmacological and immunological effects. It is also true that most current assays, which examine heterogeneity—whether aggregation or truncation or glycosylation—simply are not up to predicting safety and activity in the clinic. For example, the best current software for predicting the epitopes that antigen-presenting cells process from a protein sequence depends on knowledge of the rules of binding (recurring motifs) common among epitopes that bind the same human leukocyte antigen (HLA) groove. But these rules may not reflect the true range of amino acids that can influence T cell receptor interactions. And with more than 300 known variants each of HLA-B and HLA-DR, an extremely large number of different epitopes are present in human populations.

So what are regulators to do? If the US Biotechnology Industry Organization (BIO) has its way, nothing. In the past eighteen months, BIO has done everything in its power to filibuster and delay the formulation of an FDA approval process for follow-on biologics. It claims generic manufacturers are incapable of producing protein copies because they lack "access to the innovator's historical data, in-process and bulk product materials," thus invalidating any comparison.

But arguing on the one hand that generic manufacturers are incapable of producing an equivalent product and on the other urging the FDA to come up with an abbreviated process for brand company follow-on products is a double standard. What's more, one of BIO's principal arguments against generics—that different cell lines cannot produce equivalent products—is ironically refuted by the FDA's approval of Biogen's interferon β-1a (Avonex). This occurred despite the fact that clinical trials were conducted with a product produced from a different cell line than the one used to produce the current marketed product.

It is right that the biotech industry retains intellectual property protection and market exclusivity in return for investment in R&D. But attempts to thwart generics manufacturers on the basis of nebulous 'safety concerns' more than smacks of protectionism. Company secrecy over clinical and production details also run counter to recent calls from biomedical journals for clinical data to be lodged in centralized databases accessible to the public. It would be surely a better option for companies to lobby for expanded patent term restoration (perhaps under some form of Hatch-Waxman revisions) in return for releasing the relevant details of a manufacturing process to a generic manufacturer a short period before a brand drug's original patent is due to expire. This would provide added incentive for innovators to invest in R&D while at the same time allowing the creation of a system for generic protein approvals. The alternative is to sit tight and hope, ostrich-like, that generics go away. But generics aren't going away. And if the industry fails to find a solution, governments will find one for them.