nature biotechnology

Wrong numbers?

With biotech infiltrating multiple industries and fewer life science ventures listing on stock exchanges, what do we really learn from surveying the set of public biotech companies?

Each year, *Nature Biotechnology* trawls through the accounts of publicly quoted biotech companies and pulls out some numbers that characterize this part of the commercial life science landscape. Perhaps the most surprising statistic this year was that most of the companies that appeared in last year's survey are still there. The current straitened circumstances took their toll, of course, but total revenues were up 10%, R&D was only down 4% and the group collectively was profitable for another year. But what, if anything, does the survey tell us about the general health of the innovative life science sector?

Back in the 1990s, the answer seemed clear. Thanks to much freer flows of capital then, the annual audit measured the progress of a specialized, self-reliant and relatively independent industrial endeavor. It assessed the rapid churn of companies listing newly on exchanges. Companies could float much earlier; some were even able to go public without products in human trials. Buoyant stock markets took valuations to ecstatic heights and poured money into the sector. Product for product and dollar for dollar, biotech companies were valued much more highly than 'traditional' pharma companies.

That differential was unsustainable. As Amgen and Genentech and Biogen Idec and others climbed up the pharmaceutical league standings, reality dawned. Innovators metamorphosed into drugmakers. And as the pharma sponge absorbed more biotech, the boundaries between the two spheres faded.

The consequence of this merging is that much, if not most, of the biological products and biological techniques now resides outside the group of independent public companies that we survey. Pharma spends $65 billion a year on R&D, 25–40% of it either devoted to biological products or using the techniques of biotech. Thus, pharma outspends 'biotech,' even on biotech R&D. Furthermore, biotech processes extend far beyond the pharmaceutical segment: political imperatives and technological capability have expanded industrial biotech for biofuels production, waste management and green chemistry. Geographically, biotech is no longer a Western province: China, India, South Korea and elsewhere are prominent actors in follow-on biologic drugs, diagnostics and clinical testing.

Our public company survey reflects none of these changes: pharma companies, biogenerics firms, diagnostic and device providers all fall outside the definitions of our survey. In Asia, successful biotech companies (see p. 783) have only restricted access to mature public capital markets. Overall, the survey is now less a gauge for innovative life science and more a pointer to the shape of the Western healthcare market. To measure life sciences' impact more broadly, other indicators are needed.

To quantify innovation, we need to look, too, at activities within small private companies and, increasingly, at the early translational work in the public sector. These data are exponentially more difficult to gather than data from publicly quoted firms. Accordingly, policymakers, governments and industry associations need to devote much more effort and resources to collecting them.

MAQC-II: analyze that!

The MAQC consortium's latest study suggests that human error in handling DNA microarray data analysis software could delay the technology's wider adoption in the clinic.

Following up on its publications in *Nature Biotechnology* four years ago (http://www.nature.com/nbt/focus/maqc/index.html), the Microarray Quality Control (MAQC) consortium publishes the results of its second phase of assessment (MAQC-II) on p. 827, in conjunction with ten accompanying papers in *The Pharmacogenomics Journal* (http://www.nature.com/tpj/journal/v10/n4/index.html). The new work assesses the capabilities and limitations of microarray data analysis methods—so-called genomic classifiers—in identifying gene signatures representative of a specific pathological condition.

All in all, >30,000 genomic classifier models were built by combining one of 17 different data preprocessing and normalization methods, with one of 9 methods for filtering out problematic data, with one of >33 techniques for picking 'signature' genes, with one of >24 algorithms for discerning patterns from those genes, and with one of 6 methods for testing the robustness of the results. Thirty-six research teams sought gene signatures within 6 massive microarray datasets derived from toxicological studies of chemicals on rodents and expression profiles of human cancer patients that predict 13 'endpoints' potentially relevant to preclinical or clinical applications.

As discussed on p. 810, one key finding of MAQC-II is that the classifier models are remarkably similar in predicting outcome, irrespective of the approach used. On the other hand, the overall success of the classifiers in predicting endpoints depends on the endpoints themselves. For example, predictions were in general much worse for breast cancer and multiple myeloma, which have highly heterogenous genetic backgrounds, than for liver toxicology or neuroblastoma.

Perhaps most striking of all, some data analysis teams were consistently better at predictions than others. This may relate to simple errors associated with manipulating such large datasets. But insufficient tuning of the parameters used in a classifier model is also a likely contributor. In this sense, MAQC-II was as much an exercise in sociology as in technology. The human element in classifier implementation is key.

Thus a key take-home message is that classifier protocols need to be more tightly described and more tightly executed. In this respect, regulatory agencies and scientific journals can promote good practice. A clear need exists for greater meticulousness both in documenting the parameters of a particular classifier model used and in detailing the procedures for normalization, batch effect correction, quality control and reduction of quality control flaws. Greater attention to detail will not only enhance reproducibility of research—it will also facilitate the progression of this technology toward the clinic.