nature biotechnology

Raising the game

Last year's R&D output by the drug industry was the worst in a generation. But amid the dismal numbers, there is evidence that more innovative medicines are reaching patients.

This decade has been a disappointment in terms of the number of drugs approved each year by the US Food and Drug Administration (FDA). But 2007 will go down in history as the worst for 25 years, with only 19 new molecular entities (NMEs) registered for marketing. Prospects for a rebound in 2008 also look dim, given the relative paucity of compounds in phase 3 trials, an increasingly risk-averse FDA and a regulatory bar that is rising for NMEs with similar risk and benefit profiles to existing approved drugs. If there is a silver lining, it is that although single-year totals for approved NMEs have continued to fall, the number of biologics approved remains relatively stable. And, similar to biologics, small molecules with novel mechanisms of action appear to be making a growing contribution to total R&D output.

The bad news is that pharmaceutical productivity—measured crudely as the number of drugs approved—is only marginally better than it was back in 1983, when the industry mustered a mere 14 NME approvals. At that point, there was no 'biotech industry' to speak of; indeed, many of today's standard drug development tools were simply not invented.

It's also clear that the low number of approvals last year is no outlier. The total output of NMEs over the past three years is the worse since 1978–1980. And compared with historical averages, NME productivity over the past decade has spiralled downward (**Table 1**). In the second half of the 1990s, for example, FDA approved >30 NMEs every year. The only time in recent memory when this was achieved was 2004, when 36 NMEs were registered.

Table 1 Annual FDA approvals of NMEs

Year	NMEs approved	BLAs approved
2007	15	4
2006	17	4
2005	18	2
2004	31	5
2003	21	6
2002	16	7
2001	24	5
2000	27	2
1999	35	3
1998	30	7
1997	39	6
1996	53	3

NMEs, new medical entities (not including BLAs); BLAs, biologic license applications. Source: FDA

So why is there, apparently, nothing to show for all the technological advances that pharma and biotech companies spend so much money on developing? The answer, really, is that the whole nature of drug R&D has changed almost beyond recognition since 1983 (or even since 1993). Comparing the annual output of new drugs against this changing background is at best simplistic and at worst invalid.

One indicator of this changing picture is that the number of biologics approved has remained remarkably stable each year, and so the proportion of NME biologic approvals contributing to annual R&D output has been continuously rising.

Another very positive change is that the proportion of first-in-class molecules contributing to the total NME output is also higher than historical averages. According to a study published last month in *Health Affairs* (**27**, 33–43, 2008), between 1970 and 2000, the number of first-in-class drugs averaged about 3.5 a year. That dropped in the first five years of the decade to one per year, but it has since rebounded. In 2005, there were 7 out of 18 NMEs with new mechanisms, two years ago there were 5 out of 18 and last year there were 6. Roughly speaking, therefore, the drug development process over the past three years is producing first-in-class molecules twice as fast as it did in the previous decade.

This is a highly significant indicator of success. It is in the nature of the slow pharma R&D process that the fruits of the endeavor take time to appear. What is emerging now was started at least ten years ago.

According to *The RPM Report* (**3**, 1–12, 2008), pharma R&D spending in 1983 was ~7.5% of what it is today ($3.2 billion versus $43 billion) whereas total revenue was <10% of today's annual sales for drugs ($17 billion versus $175 billion today). Of course, dollar for dollar, drug development is now remarkably expensive and appears to be an enterprise of diminishing returns. But the nature of those returns is different. Developing first-in-class drugs involves new understanding of drug action, new screens, and new clinical trial protocols, and all of these processes carry the risks of true innovation.

At the same time, in the post-Vioxx, risk-averse universe, one must recognize that the bar for regulatory approval has been raised. If an NME is not a first-in-class breakthrough, FDA is increasingly requesting evidence demonstrating a benefit to specific populations. In the past year, for example, it turned down Sanofi Aventis' obesity drug Zimulti and requested more comprehensive safety data from Novartis and Wyeth for their respective treatments for diabetes and menopause.

The agency's increasing aversion to risk is also evident when one looks at regulatory decisions on both sides of the Atlantic. According to industry newsletter *BioCentury*, in 2007, at least eight drugs that received regulatory setbacks in the United States were approved by (or had previously received approval from) the European Medicines Agency (EMEA). In contrast, few examples can be found of NMEs given the FDA green light that were rejected by EMEA. This is particularly striking as for many years the European agency was considered more conservative and cautious than its US counterpart.

In essence then, the numbers leave us with one simple conclusion. The drop in NMEs reflects the increasing difficulty of negotiating 'me-too' drugs through FDA oversight. But an increasing emphasis on innovative drugs is assuredly in the interests of both patients and the pharma industry itself. And in today's crowded drug development environment, quality is at least as good a measure of progress as quantity.