

Macro Trends in Pharmaceutical Innovation

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A lately recycled criticism of the pharmaceutical industry is that it is failing in its mission to innovate. In particular, critics question the industry's incentives to innovate, and they deride those innovations the industry makes as imitative. Industry advocates contend the opposite.

The truth is that there are no generally accepted measures of innovation that would conclusively prove either side's point (Box 1). However, I have found trends in several measures that support both sides of the innovation debate (Cohen, 2005). Overall, the bulk of evidence suggests that the pharmaceutical industry continues to regard pioneering innovations as important (evidenced by the motivation, effort and ability of the industry to create such innovations). However, like other mature manufacturing industries, the pharmaceutical industry relies heavily on incremental innovations (what critics call "me-too" drugs) to sustain its profits. To a large extent, these incremental innovations are themselves medically beneficial and should be encouraged rather than dismissed as merely imitative (Box 2).

I will describe some of the findings that have led me to these conclusions, focusing on macro trends in major pharmaceutical industry innovation.

Is the Pharmaceutical Industry Motivated to Innovate?

Let us assume that the industry is motivated by profits

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alone, without concern for societal welfare or other motivations. Do profits alone serve as incentive for innovation in general? The answer, as provided by studies unique to the pharmaceutical industry (Roberts, 1999) and to manufacturing industries generally (OTA, 1995) is, unequivocally, yes. Profits are directly related to research and development investment (Grabowski et al, 2002), to appropriation of inventions (e.g., patents), and to innovative products themselves (OTA, 1995). The reasons for this are primarily two-fold: Innovations improve sales, both in terms of volume (Ben-Asher, 1999), by expanding the population being treated, and price (CBO, 1998). Process innovations further improve profits by reducing costs of output (FTC, 2003).

The competitive environment for new drugs has shifted in the last twenty years, causing increased pressure on firms to innovate. Changes in U.S. federal and states law in the mid-1980s spurred generic drug output. As a result, the volume share of generic prescription drugs has increased from 19% to 45% between 1984 and 2001 (PhRMA, 2003). Generic competition erodes innovators' drug profits. As profits are a primary motivator of innovation, the industry would be expected to increase its efforts to innovate in response to generics competition.

In addition to pressure from generic competition, recent evidence indicates that diminished barriers to entry have allowed "fast followers" to follow much faster than ever before (DiMasi and Paquette, 2004). As in other industries, pharmaceutical first-movers have a sustained market share advantage and at least a near-term profit advantage (Lieberman and Montgomery,

Box 1**Innovation Metrics: Quality vs. Quantity**

Assessing the quantity of innovation is relatively easy compared with measuring its quality. Industry critics have proposed schemes for lumping innovations together into buckets and labeling them (e.g., "highly innovative," "moderately innovative," etc.) sometimes using FDA's assessment of a drug's therapeutic potential at the time of NDA (New Drug Application) filing. But this approach is far from reliable and is just as subjective as selective anecdotal descriptions of innovations. A few examples illustrate this point. Which drug in each pair is more innovative?

- A reformulation of an existing cytotoxic chemotherapy that allows it to be delivered at a higher concentration over a longer duration, resulting in longer disease-free survival and reduced toxicity compared with the original formulation OR A novel, fast-tracked, priority-reviewed NME (New Molecular Entity) that was designed to supplant the original cytotoxic chemoagent and demonstrates survival improvements and toxicities comparable to that of the reformulated cytotoxic chemoagent?
- A first-in-class, priority-rated NME with identical indications for usage, and indistinguishable safety and efficacy markers, as the first four members of an older drug class OR A fifth-in-class NME that has been demonstrated to improve survival, when its four predecessors were not studied adequately to ascertain their effects on survival?
- A combination of two older drugs that has been shown to have a heretofore unexpected benefit to treat a serious disease for which neither was previously studied OR A novel, fast-tracked, priority-reviewed NME that has comparable efficacy and safety to the combination of the two older drugs?

Box 2**On the Importance of Incremental Innovation**

In its comprehensive report on commercialization of emerging technologies, the U.S. Office of Technology Assessment concluded that "In most industries, innovation proceeds in an evolutionary fashion through long periods of cumulative incremental innovation punctuated by moments of radical innovation. Though incremental innovation and adaptations of existing technology to new markets may seem mundane, they account for most innovative activity and, in aggregate, generate returns equal to those created by less frequent radical innovations." (OTA, 1995).

Speaking specifically about pharmaceutical innovation, the U.S. National Research Council noted that "Breakthrough products, which are usually the first of a class, inevitably display deficiencies after they are widely distributed. Pharmaceutical companies use these revealed deficiencies as opportunities to develop related compounds that are more effective, more selective, and less toxic" (NRC, 1996). A more recent McKinsey study concurs with these observations: "Of the 32 [blockbuster] drugs introduced over the past decade, only a quarter targeted novel mechanisms of action... Some of these were "me-too" compounds, but a majority had at least one source of significant

clinical differentiation..." (Booth and Zimmel, 2004).

As Wertheimer and colleagues have observed: "The therapeutic power, stability, and utility of a [drug] class are defined through the contributions of its multiple agents... [Therefore,] the collective therapeutic advantage of the class as a whole may be of greater clinical significance than the original advantage of the pioneer compound" (Wertheimer et al., 2001).

Ironically, the radical innovation collectively described as "personalized medicine" is dependent on incremental innovations -- in the form of expansions in the members of each drug class. Offering choices requires choices to offer.

Finally, whether one accepts evidence pointing to the medical and social importance of incremental innovations or not, because of their inherently lower risk and cost basis, incremental innovations are an important source of industry revenues and profits and thus an important source of research and development funds. If policy changes dry up the flow of incremental innovations -- absent an alternative mechanism for replenishment -- the R&D well will inevitably run dry and along with it the resolve of this industry to pursue pioneering innovations.

1998). The industry has responded to these incentives by turning modern pharmaceutical drug development into a race to be first-to-market.

The Industry's Capacity for Innovation: Patents

The pharmaceutical industry relies heavily on patents to appropriate its innovations (Roberts, 1999; FTC, 2003). As the U.S. Office of Technology Assessment has described: "Patents were designed to promote innovation by providing the right to exclude others from making, using, or selling an invention. They enable innovators to obtain greater profits than could have been obtained if direct competition existed. These profits act as incentives for innovative activities" (OTA, 1981). Patents are an imperfect but oft-used metric of innovation capacity.

U.S. pharmaceutical patent activity, relative to overall U.S. patent activity, increased beginning in the mid-1990s. Prior to that time, it had been stable, at least as far back as 1976. The increase in activity appears to have been largely due to an increase in biotech-related patenting rather than an increase in patents on small-molecule drugs (data not shown). Consistent with this notion, the patent activity appears to be largely due to an increase in patenting by universities and colleges. Patent activity by major pharmaceutical companies decreased relative to other assignees during this period (Figure 1). The finding of reduced drug patenting by the majors is consistent with observations that, as industries mature, their leaders tend to diversify their patent output beyond the industry's original activities (McGahan and Silverman, 2001). The current study did not track patenting in areas where these industry leaders might have diversified their efforts, such as research

technologies, medical devices and clinical diagnostics.

The Industry's Capacity for Innovation: Research & Development

The pharmaceutical industry spends more on R&D as a percent of gross output than any industry except aerospace (NSF, 2004). Pharmaceutical industry R&D expenditures, as reported from the Pharmaceutical Research Manufacturers of America (PhRMA, 2004) Annual Survey increased exponentially from 1970 to 2001, with some evidence of spending growth modera-

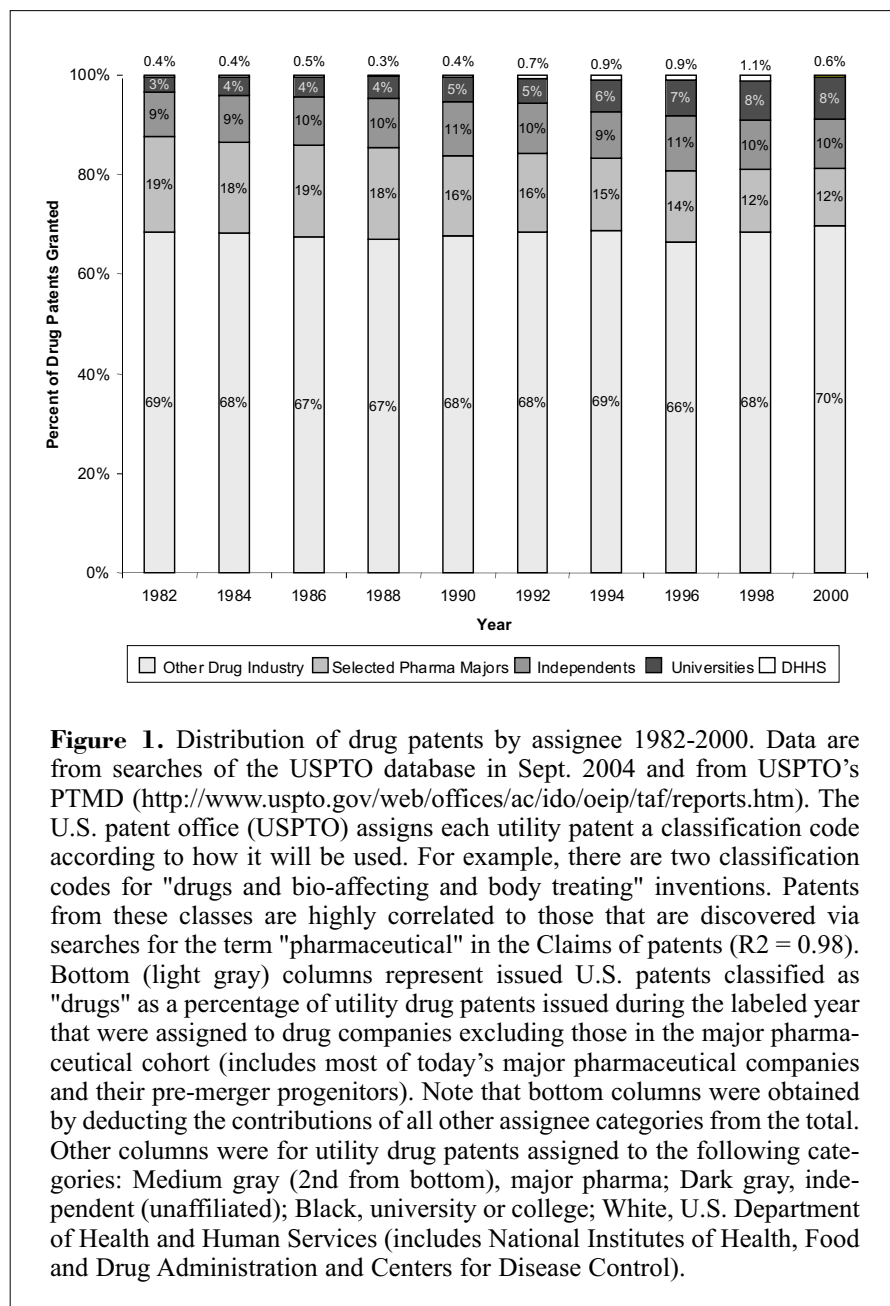


Figure 1. Distribution of drug patents by assignee 1982-2000. Data are from searches of the USPTO database in Sept. 2004 and from USPTO's PTMD (<http://www.uspto.gov/web/offices/ac/ido/oeip/taf/reports.htm>). The U.S. patent office (USPTO) assigns each utility patent a classification code according to how it will be used. For example, there are two classification codes for "drugs and bio-affecting and body treating" inventions. Patents from these classes are highly correlated to those that are discovered via searches for the term "pharmaceutical" in the Claims of patents ($R^2 = 0.98$). Bottom (light gray) columns represent issued U.S. patents classified as "drugs" as a percentage of utility drug patents issued during the labeled year that were assigned to drug companies excluding those in the major pharmaceutical cohort (includes most of today's major pharmaceutical companies and their pre-merger progenitors). Note that bottom columns were obtained by deducting the contributions of all other assignee categories from the total. Other columns were for utility drug patents assigned to the following categories: Medium gray (2nd from bottom), major pharma; Dark gray, independent (unaffiliated); Black, university or college; White, U.S. Department of Health and Human Services (includes National Institutes of Health, Food and Drug Administration and Centers for Disease Control).

tion more recently. R&D spending as a percentage of net sales, conversely, was stable until the latter half of the 1970s and then increased linearly until the mid-1990s, where it initially stabilized and now appears to be diminishing slightly. So, while the industry was enthusiastically returning an increasing proportion of its revenues to R&D throughout much of the last thirty years, it now appears to be less inclined to do so.

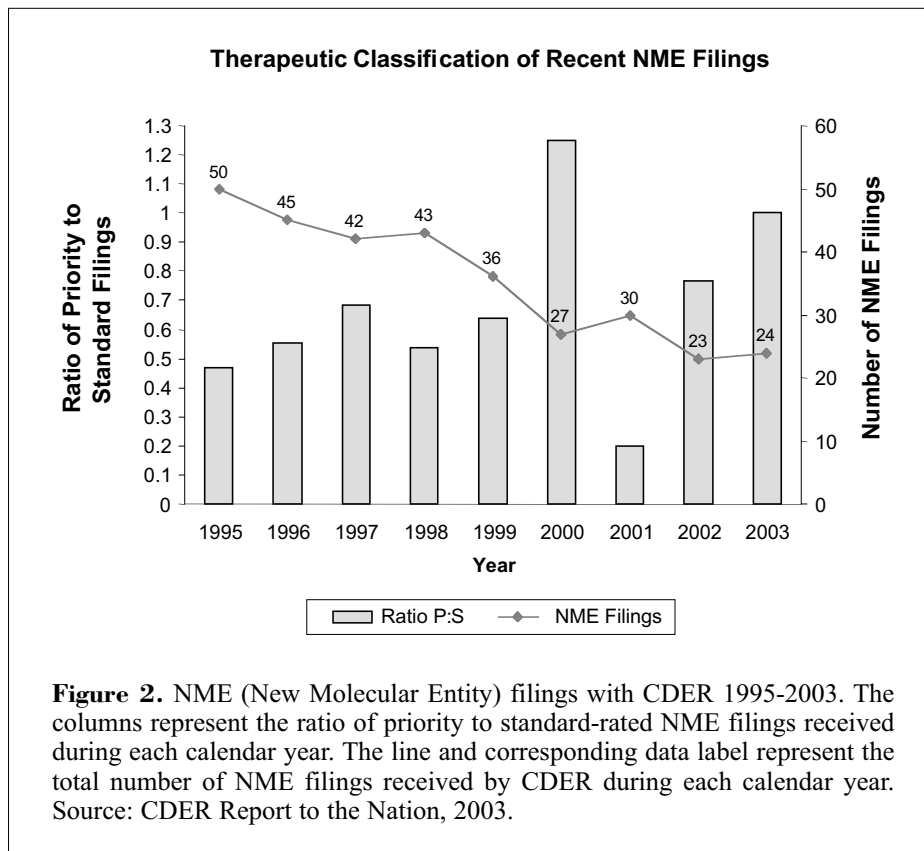
R&D spending by the pharmaceutical industry was compared to other industries using the National Science Foundation Survey of Industrial Research and Development as the data source. Throughout the 1970s and early 1980s, pharmaceutical R&D spending generally exceeded aggregate industry spending by a ratio in excess of 3:1. Following this period there was a brief lull in relative R&D spending by the pharmaceutical industry, followed by a surge in 1993 and then a return to the relative strength of the 1970s period.

Personnel are another surrogate of R&D investment. The NSF survey allows an examination of R&D investment in personnel who are primarily responsible for performing the experiments and developing the processes that lead to drug innovations. The pattern of

employment of scientists and engineers in the pharmaceutical industry largely parallels the R&D expenditures as a percent of net sales. Furthermore, the ratio of pharmaceutical industry employment of scientists and engineers exceeds aggregate industry employment of such personnel by about the same ratio as pharmaceutical industry R&D spending exceeded aggregate industry R&D spending (i.e., ~2:1 to ~3:1).

Innovation Output: the Recent Past and Present Drug Approval Trends

Between 1990 and 2003, the Center for Drug Evaluation and Research (CDER) at FDA approved 1,171 New Drug Applications (NDAs). Of these, 400 (34%) were New Molecular Entities (NMEs, defined as an active ingredient that had never previously been marketed in the U.S.) and 771 (66%) were non-NMEs. Most commonly, non-NMEs refer to new formulations of previously approved active ingredients. Of the NMEs approved, 166 (41% of NMEs) were granted priority review status, compared with 98 (12.7%) priority-status non-NMEs. With the exceptions of 1996 and 1997, which were particularly productive years for standard-rated NDA approvals, NDA approvals were generally stable throughout this interval.



In contrast to NDA approvals by CDER, the majority of which were for small-molecule drugs and diagnostics, BLA (Biologics License Application) approvals for recombinant protein drugs by the Center for Biologics Evaluation and Research (CBER) increased during this interval (from 11 between 1989 and 1996 to 17 between 1997 and 2002). The majority of BLA approvals for therapeutic proteins were granted to "biotech" firms (17/28) more often than to traditional pharmaceutical firms (11/28), but there was no trend suggesting a change in the innovators of such drugs with time (Reichert and Paquette, 2003).

The priority review classification

provides a sense of FDA's judgment of the value of a new drug or use as it relates to previously approved drugs at the time of NDA filing. There has been a pronounced decline in recent NME filings with CDER, from 50 in 1995 to 24 in 2003 (Figure 2). However, the ratio of priority- to standard-rated filings increased year over year for six of the eight years in this series. In 2003 there were as many priority-rated filings as standard-rated.

Beginning in fiscal year 1993, FDA began tracking filings and actions taken on supplements to original NDAs (i.e., efficacy supplements) separately from other NDAs. Efficacy supplements are filed when a new or modified indication or label change with new efficacy data is sought by the original manufacturer for previously approved drugs. In contrast to NME filings, which declined in the last decade, efficacy supplement filings increased markedly, reaching a peak of 175 during FY 2000, a 90% increase over FY 1993 filings (Figure 2). More recently they have moderated slightly but still remain 42% higher than 1993.

The proportion of efficacy supplement filings granted priority review designation has also increased. While just 7% of efficacy supplement filings were designated as priority in 1997, 19% were so designated in 2002 and 2003. Therefore, there is no evidence to support the criticism that the industry in general has focused its recent development efforts on minor modifications to existing drugs that have little social utility. Indeed, available data suggest the opposite.

Innovation Output: the Future?

Having a glimpse of what is "on the horizon" is perhaps the only advantage to a protracted product development cycle. A sampling of a proprietary investigational drugs database at approximately the same time each year since 1995 indicates annual increases in Preclinical, Phase 1 and Phase 2 projects without a concomitant increase in Phase 3 projects (Parexel, 2004). This is the Phase 2 roadblock that

industry veterans speak of, the reasons for which remain unknown.

Using another investigational drugs database (R&D Directions, 2004) and assuming recent historic success rates for U.S. marketing approval, a total of approximately 370 new drugs (about 50% NMEs) could be approved by FDA within the next three to four years. This could represent as much as a 70% increase in innovative output as compared with the 2001-2003 period.

Conclusions

Competitive pressures provide a profit motivation for pharmaceutical industry innovation. The evidence from R&D expenditures, allocation of R&D resources, and drugs being produced, together support the industry's ongoing commitment to innovate. Fewer NMEs are being approved, including fewer "priority-rated" NMEs. But based on NME filings, the decline in priority-rated NME approvals does not appear to be related to an industry aversion to developing drugs destined for a priority review, as the proportion of NME and efficacy supplement filings that receive this rating has been increasing, not decreasing, recently. Finally, the future looks brighter in terms of innovative output, with the possibility for large relative increases in new drug approvals over the coming few years.

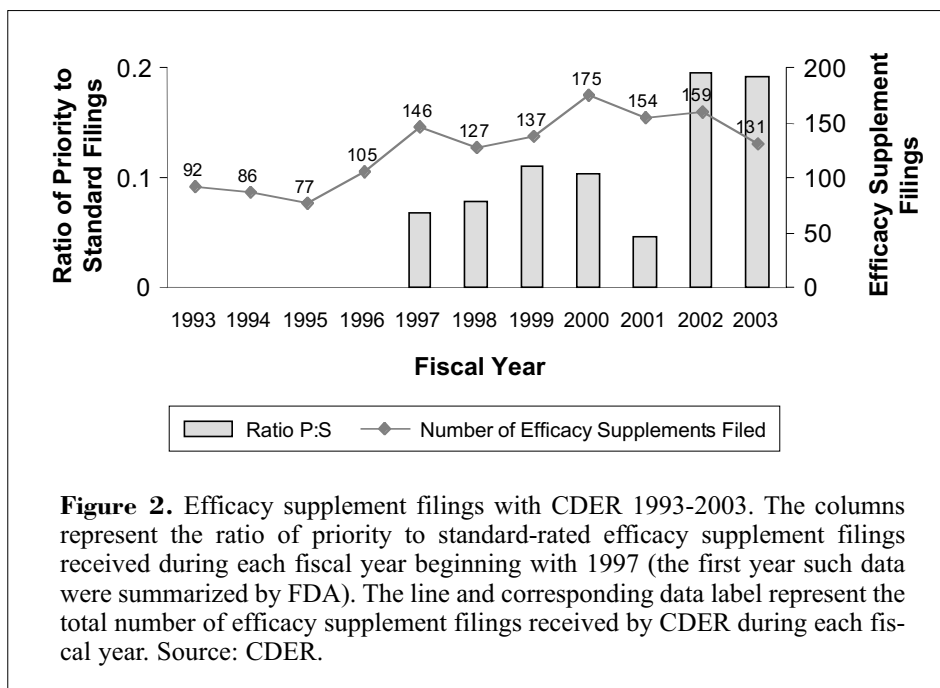


Figure 2. Efficacy supplement filings with CDER 1993-2003. The columns represent the ratio of priority to standard-rated efficacy supplement filings received during each fiscal year beginning with 1997 (the first year such data were summarized by FDA). The line and corresponding data label represent the total number of efficacy supplement filings received by CDER during each fiscal year. Source: CDER.

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