Drug innovation and public policy: some speculations

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Intelligent policy making about prescription drugs in the United States has for some years been hampered by, on the one hand, the Knee-Jerk Paranoid school of analysis, which views the industry as the corporate embodiment of the leeches whose therapeutic turf they have taken over, and, at the opposite extreme, the Knee-Jerk Boosterism contingent, depicting the industry as the incarnation of Hygeia, the font of nearly all that is good and healthful in the American system of medical care. Clear thinking about the important opportunities and challenges facing us in relation to drug policy obviously requires the greatest possible distancing from both extremes. It is certainly true that prescription medicines, when used appropriately, represent one of the “best buys” in modern health care delivery, as well as any other sector of the economy. It is indeed wonderful that our society has discovered precisely which chemicals, swallowed or injected, can cure pneumonia, prevent strokes, alleviate pain, strengthen the heart, and literally restore sanity to the insane. Considering the enormous cost of such illnesses in human as well as dollar terms, these products would be a bargain even at multiples of their current price.

Nurturing Pharmaceutical Innovation

Important as this point is, however, it must be counterbalanced by other considerations in formulating a coherent national policy on pharmaceutical innovation and regulation. At its root, the question underlying this issue is one of the most important a society can face: How is it possible to nurture innovation, and what are the rights and responsibilities of all parties concerned? The issue presents itself in one of its most interesting forms in regard to pharmaceutical development, but in many important respects this example is not totally different from innovation in many other aspects of technology and culture, from semiconductors to the arts. Innovation of all kinds is a costly undertaking, both in terms of dollars and—probably more importantly—in terms of risk. Innovation is the driving force behind science, aesthetics, and ultimately the economy as well. Figuring out how to nurture the individuals and concerns which
choose to occupy this vital but dangerous societal niche is one of the most important challenges a free society faces.

It has become traditional for representatives of the pharmaceutical industry to present the drug development process as if it were totally different from innovation in other sectors of human endeavor. There is one major difference, that new products from the drug industry must undergo lengthy and costly clinical testing and regulatory approval prior to marketing, a fate quite different from that facing most other innovations. This difference was relevant to the debate that occurred in 1982 about the proper length of patent protection that should be accorded new drugs, with the industry correctly pointing out that many years of the seventeen-year term of patent protection were, in the case of medications, eroded by the requirement of premarketing testing and regulatory review. The Patent Term Restoration Act of 1982 was a plausible response to that difference, adding back years of patent protection that would otherwise have disappeared.

However, aside from these differences in the hurdles which must be jumped prior to entry of a new product into the marketplace, it is not at all illogical to consider innovation in drugs in relation to innovation of other sorts. The preoccupation of the research-intensive drug companies with the “imitation” manufacturers (their value-laden term for those who make generic drugs) is an interesting case in point. When was the last time that the chief executive officer of IBM or Apple publicly decried the proliferation of “imitation” personal computers? Should the Ford Motor Company have been protected against the “imitators” at General Motors? Have the surgeons who developed coronary artery bypass surgery or angioplasty retained lobbyists to fight off the proliferation of those who want to learn how to replicate these procedures for the benefit of larger numbers of patients?

No, other industries and innovators seem comfortable with eventual passage of their innovations into the public domain either rapidly in the case of nonproprietary innovators, or after a suitable period of restricted ownership. It is not hard to imagine the paralyzing effect on further innovation, competition, and pricing if the sole right to produce certain products, such as light bulbs, ball bearings, or transistors had been left in the hands of the original inventors for longer periods of time than our centuries-old patent system permitted. A society benefits from the protection of its innovators for a limited period of time, and then benefits again when the innovation is opened up into the push and pull of the marketplace.

Why should innovation in pharmaceuticals be different, particularly with the additional protection afforded by the Patent Term Restoration Act? To hear the situation described by some industry spokespeople, one would think that the rate of innovation and level of profitability for
the drug industry were in need of intensive care. Yet a very different picture, and a more accurate one, is presented in the stock prices and annual reports of these same corporations. The drug industry even sustains an added bonus not generally given to other industries: the prolongation of profits from a given product through the phenomenon of “effective patent life.” Even when a patent has expired for a particular medication, doctors and patients alike may well continue to prefer the brand-name version, even though much more inexpensive and equally effective generic versions come onto the marketplace. Librium (chlordiazepoxide), the famous tranquilizer marketed by Hoffman-La Roche, is a classic case study of this phenomenon, and one might expect that Valium (diazepam), also from Hoffman-La Roche, will experience a similar fate as its patent expires. Nor is it the case that a patent is a patent is a patent. Teams of clever chemists and lawyers have devised ways of weaving patents around patents that can add years of life to corporate ownership over a particular product.

Facing Economic Pressures

What, then, is behind the concern that the income needed to fuel new drug research is in jeopardy? It is not surprising that the pharmaceutical industry is feeling itself under increasing pressure in relation to its future revenue streams. Although sales and earnings per share have not yet reflected it, in the next few years drug companies will be hit by massive and unprecedented economic pressures as the United States (as well as an increasing number of third world nations) takes increasingly coherent action to limit health care costs. One of the first casualties will probably be costly prescription medications for which equally effective alternatives are available. This will entail therapeutic substitution as well as generic substitution. (“Therapeutic substitution” is the process through which a physician or, in some more brazen situations, a pharmacist is encouraged not only to choose the generic version of a given chemical entity, but instead to choose a slightly different chemical entity for the treatment of a patient, if the chosen product has very similar therapeutic properties but is less costly.) Some major changes will need to occur before such product selection begins to affect the industry in a massive way, and these are currently in process. One is prospective payment for health care services, on the basis of a given diagnosis or simple capitation. Hospitals—or health maintenance organizations (HMOs), or insurers, or employers—thus come to be at risk for every potentially unnecessary cost incurred in the care of patients, and the use of an expensive medication when an inexpensive one will work exactly as well is one of the more attractive candidates for such cost cutting.

In the past, many individual physicians have shown a soft spot for the
research-intensive pharmaceutical companies by prescribing their drugs preferentially, often with the sense that in doing so they were helping maintain the revenue stream that would go to produce future new products. Laudable as this practice may or may not have been (it was, after all, not the physician’s money that was being spent) it is difficult to imagine a hard-pressed hospital, or Blue Cross, or a large HMO chain acting out of the same allegiance. In my own days as an intern not long ago, the relative cost of different medications was not something we ever needed to think about. Now, in 1986, I find myself developing a program designed to bring such factors into consideration in therapeutic decisions at one of the major Harvard teaching hospitals, the Beth Israel in Boston. Optimal care of the patient, of course, comprises the first, second, and third considerations; but now, somewhere on the list in the agenda for clinical decision making is the cost issue, and quite appropriately so.

At the other end of the spectrum in terms of technological intensity another important trend is developing. Increasing numbers of third world countries are attempting to get the most effect for their very limited health care budgets by reducing expenditures on costly medications for which less expensive alternatives exist. This is altogether understandable in poor nations which may be spending an astoundingly high proportion of their scarce health care resources on antibiotics and other costly drugs which are often not even used appropriately, but nonetheless consume resources that are desperately needed in other areas of the health sector. National formularies are being put in place and enforced at an unprecedented rate, spurred on in many cases by the World Health Organization’s Essential Drugs Program.

In the late 1970s, we initiated a program of "academic detailing" in which medical school-based educators went forth to teach physicians about the disadvantages of some commonly prescribed medications, much as industry-supported sales representatives have traditionally gone door-to-door to encourage physicians to prescribe their company’s products. As one would expect from the major commitment industry has made over the years to such an approach, it does turn out to be a powerful means of changing prescribing, and one that is cost-effective for the public sector as well, as documented in several recent studies. It is indeed a sign of the times that this approach is now being taken up by HMOs, tertiary care hospitals, and developing countries alike as a means of providing a more balanced set of influences on the prescribing physician. We can only expect to see more of this in the future. Such “educational outreach” may well improve the quality of care if it is done well; it will certainly lower drug expenditures now that the clear economic incentive exists to do so. Inevitably, this will cut into pharmaceutical sales, especially at the high end of product lines.

Offsetting these major changes in the way health care is paid for and
clinical decisions are made will be the countervailing demographic changes the western world is experiencing. Vastly increasing numbers of elderly patients will expand the markets for medications of most kinds at the same time that the factors described above will be imposing greater selectivity on prescribing. There is no way to predict which effect will predominate, but available evidence seems to suggest that increased selectivity by prescribers will have a greater economic impact on the pharmaceutical industry than will increasing numbers of patients.

**Transforming Pharmaceutical Research**

If these economic forces are indeed lining up as described, then is pharmaceutical research “an endangered species?” Yes and no. Yes, in that there will clearly be some impact on cash flow from the prescribing belt-tightening that will be occurring in the coming decade. It will be far more difficult for product development to rely even in part on revenues dependent upon inefficient prescribing patterns in the third world or at home. However, innovation will not become extinct, but rather will need to undergo some evolution, a generally favorable process which organizations and species experience when selection pressures become intense. “Endangered species” throughout history have had to learn new ways of adapting if they were to survive, and scarcity of resources has been one of the most compelling effectors of such evolution. The transformation could occur in several ways.

**Better targeting of innovation.** While no drug company sets out with the hopes of developing a mediocre product, it is nonetheless striking how many independent efforts have occurred in the last decade to develop “me-too” versions of various commercial favorites, such as non-steroidal anti-inflammatory drugs (NSAIDs) and beta-blockers. True, some of these products did turn out to have advantages, but many were clinically indistinguishable from products already on the market. In many instances, the likelihood may be high at the outset that trivial manipulations of salts or side chains will enhance a product’s patentability, but are unlikely to strengthen the therapeutic armamentarium. Economics may dictate that if funds for new product development do become more scarce, anticipatably trivial manipulations will be the first activity to be abandoned.

**Streamlining the regulatory process.** While the “drug lag” between Europe and the United States is, thankfully, no longer the subject of considerable media attention, it remains the case that the Food and Drug Administration (FDA) bureaucracy should be capable of more efficient processing of new drug applications than it is at present, without any diminution in the care which such applications receive. It is an ironic aspect of the current deregulatory “lean government” movement in Wash-
inong that some regulatory activities are being made even more cumbersome by inadequate staffing and reduced budgetary support for certain agencies, such as FDA. Less support for regulatory agencies does not necessarily lead to greater regulatory efficiency, and this point needs to be given more attention by the current administration.

**Other sources of innovation.** Industry spokespeople correctly point out that much pharmaceutical innovation has been the result of work by the research-intensive, privately held drug companies, not government or academia. There is considerable truth to this, but there is a bit more to the picture. First, while such companies are to be commended for the investment many of them have made in research, it is nonetheless the case that an enormous share of the basic biological research which underlies so much of new drug development is funded by the federal government and conducted in universities. One can only wonder what the current proposed restrictions on federal funding for the National Institutes of Health (NIH) will mean for the further flowering of such basic research several years (or even decades) from now.

While it has been the case that thus far the bulk of productive product development has come from industry, it is not inconceivable that in the future other sources might emerge. After all, an enormous amount of important innovation in health care technology—including new kinds of surgery, diagnostic procedures, and radiation therapy, to name but a few—have been the result of efforts in universities, teaching hospitals, and the NIH rather than industry. Should the pharmaceutical industry decide that the return on investment for the development of new drug products is less attractive than the return available from other commercial activities into which they might diversify, whether home care services, “wellness” programs, or fast food chains, there are many very capable minds that would be more than equal to picking up the challenge. In another political climate, one can even imagine a program of federal sponsorship of targeted pharmacological research akin to the billions of dollars currently being spent on federal sponsorship of other forms of medical research, with results that have been quite impressive.

But it will not, in the end, come to that. If return on investment for new drug development dips below levels that can be achieved in other sectors of the economy, and if this in turn results in a reduction in product innovation (although there is no convincing evidence that either of these is occurring, or about to occur), market forces will likely respond by increasing the return for those who continue to develop better products. This would mean, of course, that the prices for new drugs would go up, often dramatically. Since this will be occurring at a time when pressures will also be mounting for greater selectivity in drug choices in order to reduce expenditures in the health sector, such costly “breakthrough” drugs will increasingly be used only in clinical situations in which they
are clearly superior to less expensive agents already on the market. This will make it much more difficult for companies to do a large volume business with breakthrough drugs in order to recapture their development costs (as was the case with the truly innovative and extensively overutilized anti-ulcer drug, cimetidine). Inevitably, this will boost the price of such innovative drugs even more, further feeding into the cycle of high cost–greater selectivity–higher cost, and so on. The result of these trends is that, ultimately, we will be paying much more for the fruits of pharmacologic research, but far more selectively. New payment mechanisms will need to be put into place to ensure that those patients who truly need such costly medicines will be able to get them.

To pursue the “endangered species” metaphor beyond all reasonable limits, one could point out that when ample vegetation became too scarce to support the mammoth caloric needs of the dinosaurs, they did in fact cease to exist. In doing so, however, they opened up an ecological niche for mammals which were much smaller, far more agile, and capable of adapting to a more challenging environment. Those mammals, in turn, gradually evolved into humans. The good news for all of us is that the research-intensive pharmaceutical companies are not likely to go the way of the dinosaurs. Industry leaders should find considerable comfort in the fact that unlike organisms, organizations can occasionally undergo substantial self-transformation within the space of one generation as they attempt to meet the demands of a changing environment.