Reexamining drug regulation from the perspective of innovation policy: comment

Zweifel, P
Reexamining drug regulation from the perspective of innovation policy: comment

Abstract

This is a very colorful paper that makes for interesting reading. The author shows that the U. S. Food and Drug Administration (FDA) increasingly does not decide about market access to drugs only, but influences the innovation process as a whole. And although "information" does not appear in the title of the paper, the distribution of knowledge as affected by the FDA plays an important role at several stages of this process. For this reason, the body of this commentary is arranged according to the stages of the innovation process.
Reexamining Drug Regulation from the Perspective of Innovation Policy

Comment
by
PETER ZWEIFEL

1 General Remark

This is a very colorful paper that makes for interesting reading. The author shows that the U.S. Food and Drug Administration (FDA) increasingly does not decide about market access to drugs only, but influences the innovation process as a whole. And although “information” does not appear in the title of the paper, the distribution of knowledge as affected by the FDA plays an important role at several stages of this process. For this reason, the body of this commentary is arranged according to the stages of the innovation process.

2 Issues Addressed with Respect to the Innovation Process

2.1 FDA and the Supply of Biomedical Information for Drug Development

Research divisions in large pharmaceutical companies pose particular incentive problems because employees hardly bear any of the considerable risks. Therefore, companies have tended to outsource this function. The first stage of the innovation process thus frequently amounts to the purchase of biomedical information for drug development. Here, the paper makes a nice point: Patent protection also applies to this biomedical information, thus raising the cost of drug development to pharmaceutical companies rather than just increasing future returns on the finished product. At this juncture, the reader would be interested to know whether and how the FDA is involved in the regulation of the marketing of these information products as well, or whether this remains exclusively within the authority of the Patent and Trademark Office (PTO).

2.2 FDA and Patent Protection of the Innovative Drug

Patent protection has several dimensions, and the FDA has come to modify several of them.
2.2.1 Geographical Dimension of Patent Protection

Here, one has to distinguish between the national and the international exhaustion of patent rights. The U.S. imposes national exhaustion, which means that a protected product can be resold at the reseller’s terms and conditions only within the U.S. The EU Commission, by way of contrast, imposes international exhaustion because of its quest for the realization of a single market. One might note that the underlying issue is whether the property right conferred upon the inventor is simply to set one monopoly price or to devise a schedule of differentiated prices. Price discrimination by pharmaceutical innovators according to willingness to pay in EU member countries may well be efficiency-enhancing to the extent that it mimics Ramsey pricing, which guarantees the recovery of the fixed cost of drug development while minimizing the distortion caused by deviating from the “price equals marginal cost” rule (DANZON [1997]).

The Prescription Drug Marketing Act of 1987 prohibits re-importation of drugs to the U.S. except by the manufacturer, who therefore is enabled to practice international price discrimination. The FDA is not directly involved in the geographical dimension of patent protection. Still, by admitting a new drug to the U.S. market, it does emit a signal that is very valuable to an innovator that intends to sell its product worldwide.

2.2.2 Temporal Dimension of Patent Protection

It is in this dimension that the FDA has become an important player. In 1983, it was directed, pursuant the Orphan Drug Act, to grant seven years of market exclusivity for products for the treatment of rare diseases. As noted by Rebecca Eisenberg, this has the same effect as patent protection. In 1984, the Hatch–Waxman Act involved the FDA in the actual distribution of knowledge, in that on the one hand FDA was to accept Abbreviated New Drug Applications (ANDAs) filed by generic producers, and on the other hand it was to stay an ANDA approval for 30 months if the patent owner filed an infringement action. The Act also provides three years of market exclusivity to an already approved product if it is changed in ways that require new clinical trials. Because the Act at the same time required the PTO to increase patent protection by a maximum of five years in order to make up for the delays in FDA approvals, its combined effect may well be to extend the effective life of pharmaceutical patents in spite of the ANDA option. Finally, the Food and Drug Administration Modernization Act of 1997 directs the FDA to grant an additional six months of exclusivity if a drug has to undergo pediatric trials.

It may be worthwhile to consult economic theory to see whether these modifications might have anything to do with efficiency considerations. A simple yet informative model by DE BROCK [1985] depicts effective patent life as the outcome of a non-cooperative game played by the patent authority (complemented by the FDA in the present case) and the innovator. The patent authority seeks to maximize the sum of private benefits (profits accruing to the innovator) and social benefits (surplus available to the consumers of the new drug). DE BROCK [1985] shows that
given credible assumptions, the authority tends to keep the effective patent life as short as possible. However, it is constrained by the innovator’s reaction function, which implies that it takes some minimal effective patent life for any innovative effort to occur, and an extension to call forth additional innovative effort. The authority’s optimum is where its indifference curves in \{innovative effort, patent protection\} – space runs tangent to the innovator’s reaction function in the same space; this optimum may be considered efficient to the extent that the authority’s utility function correctly mirrors society’s concerns.

This model is extended in ZWEIFEL AND BREYER [1997] to predict adjustments to exogenous shocks. Three such changes are displayed in Table 1. The first is increased marginal cost of innovative effort – e.g., because of higher administrative hurdles [item (a)] – a credible development because the FDA’s documentation requirements have increased over time. The predicted optimal adjustment is to increase patent life. The patent restoration provision of the Hatch–Waxman Act can be interpreted in this light. Its provision to grant another three years of protection for conducting additional clinical trials simply to modify a previously approved product may still be an adjustment in the interest of efficiency, although a more differentiated clause would have seemed more appropriate. However, it is questionable whether the FDA Modernization Act, singling out drugs with pediatric trials, can be viewed as efficiency-enhancing.

### Table 1

<table>
<thead>
<tr>
<th>Exogenous change</th>
<th>Likely change of equilibrium</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Higher marginal cost effort of innovation, due, e.g., to administrative hurdles</td>
<td>Increase patent life (Hatch–Waxman Act: patent restoration, 3 years for new clinical trials; FDA Modernization Act?)</td>
</tr>
<tr>
<td>(b) Lower marginal revenue of innovation effort, due, e.g., to more parallel imports under international exhaustion of patent rights</td>
<td>Increase patent life (Prescription Drugs Marketing Act; Orphan Drug Act?)</td>
</tr>
<tr>
<td>(c) Increased relative weight of marginal social benefits in authority’s utility function</td>
<td>Decrease patent life (Hatch–Waxman Act: ANDAs)</td>
</tr>
</tbody>
</table>

The second change is a drop in marginal revenues associated with innovative effort, which is unrelated to its productivity in terms of discoveries [item (b) in Table 1]. An increase in parallel imports is a case in point. The predicted optimal adjustment
again is an extension of patent life. The Prescription Drug Marketing Act fits this prediction, although (dating from 1987) it is more of a reaction to parallel imports from Canada than to the EU’s quest for a single European market and its preference for international exhaustion of patents, which only started at that time. Whether the Orphan Drug Act also falls in this category is less clear, because drugs designed for the treatment of rare diseases have always tended to feature low marginal returns to innovative effort.

The third exogenous change may be an increased weight of social benefits compared to the innovator’s private benefits in the patent authority’s (or ultimately the legislators’) utility function [item (c) in Table 1]. Rebecca Eisenberg’s account emphasizes the desire to gain access to cheaper generic drugs earlier, possibly in the interest of consumers, but even more likely in the interest of legislators who vie for budgetary relief of the two public health insurance schemes Medicare and Medicaid. This seems to be the rationale for the ANDA provision of the Hatch–Waxman Act, which results in a shortening of effective patent life.

2.2.3 Institutional Dimension of Patent Protection

The author sees some merit in having both the TPO and the FDA involved in the determination of effective patent life. Her position can be examined with reference to Table 1, whose entries are to be understood as also saying that the more marked any of the three changes (a) to (c) is, the more marked the adjustments should be to be efficiency-enhancing. Now it may well be true that the FDA is better capable than the PTO of estimating the magnitude of these changes. It should thus also be better capable of effecting adjustments of the appropriate magnitude.

However, the relevant decisions were made in the legislature. In all instances cited in the paper, legislation created a rather rigid mandate for the FDA, leaving little room for bringing to bear FDA’s superior knowledge. Therefore, the question of why there should be another authority for the fine tuning of effective patent life in the case of pharmaceuticals remains a somewhat open issue. One can of course still argue that administrative expedience calls for such fine tuning by the FDA, but then this advantage would have to be weighed against the risk of capture, which presumably is higher for a regulatory authority specialized in one single industry.

2.3 FDA and Post-Marketing Surveillance

The final stage of the innovation process of possible relevance to the FDA is post-marketing surveillance. Since the FDA’s primary responsibility continues to be to determine the health and safety effects of a new drug, one would expect it to be active in the monitoring of these effects after market launch. FDA could not only use the same criteria for granting and revoking market access, but could also collect the same type of information, for the evaluation of which it has comprehensive know-how. Indeed, pursuant to the FDA Modernization Act of 1997, FDA has introduced “fast track” procedures in combination with post-marketing studies. However, the
author notes that companies’ compliance with post-marketing requirements has been poor. It would be interesting to know whether the FDA lacks the authority to revoke marketing approval or refrains from using this sanction in actual practice.

The paper describes how the National Institutes of Health stepped in with a large-scale study of the effects of hormone replacement therapy in women. The question remains why such a study was not carried out or at least commissioned by the FDA. Is evaluating the evidence from clinical trials so different from evaluating the evidence from post-marketing studies? Or would the FDA as the regulator be challenged for picking out one product rather than another for monitoring, its capacity being insufficient to cover all products approved?

These considerations highlight the fact the comprehensive monitoring of the health effects of drugs is very costly. Rather than dwelling on the division of labor between the FDA and the National Institute of Health, both of which are public entities, one might therefore consider a larger degree of involvement of private actors, viz. the patients themselves. At least as far as negative side effects are concerned, patients would select those instances they deem important enough to justify instigating a liability suit. In order to limit their financial risk, the burden of proof could be shifted to the defendant. In Japan, this shift was in fact undertaken with regard to environmental impairment during the 1970s and to adverse drug reactions during the 1980s (AWAJI [1989]). Of course, such a shift would cause a slowdown in the process of pharmaceutical innovation; on the other hand, it would serve to internalize the external costs of this process in a rather targeted way.

3 Final Evaluation

This paper gives a vivid account of how an institution (the Food and Drug Administration in this case) whose original mission was to gather information for assessing the health and safety characteristics of an innovation is mandated to allocate this information between the innovator and the imitator. This has resulted in effective patent protection of new drugs being decided upon by two authorities, viz. the Patent and Trademark Office and the FDA. The paper justifiably raises doubts concerning the efficiency properties of some of the legislation that tends to extend patent protection. It is less sceptical about FDA’s concomitant dual mission. Yet, the FDA seems to have little flexibility to accommodate the (possibly changing) trade-off between its traditional patient protection objective and its new drug innovation objective. Dual missions of this type constitute an important issue of institutional design that would merit further research.

References


Peter Zweifel
Socioeconomic Institute
University of Zurich
Hottingerstr, 10
8032 Zurich
Switzerland
E-mail:
zweifel@soi.unizh.ch