

# Branded Versus Generic Competition? A Kind Word for the Branded Drugs

By RICHARD A. EPSTEIN\*

## I. Danger in Transition

Transitions are times of danger in virtually all areas of human life. More accidents are likely to occur when cars go in and out of parking spaces, or when planes take off or land.<sup>1</sup> More medical mishaps are likely to happen in hospitals when there is a change in shifts between nurses.<sup>2</sup> The same pattern holds in the law of pharmaceutical patents, during the transition from a fully proprietary regime to one that allows for as many firms as possible to market a generic version of a once-protected pharmaceutical patent.

The difficulties of this system were made evident in the lengthy discussion of the six month coexclusivity period under the Hatch-Waxman Act<sup>3</sup> that has been extensively discussed in many articles.<sup>4</sup>

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\* Laurence A. Tisch Professor of Law, New York University School of Law, the Peter and Kirsten Bedford Senior Fellow, The Hoover Institution, and a senior lecturer at the University of Chicago. My thanks to Isaac Gruber, the University of Chicago Law School, class of 2012, for his usual excellent research assistance.

1. See Mike Antich & Lauren Colin, *Accident Management: Costs Trending Upward*, AUTOMOTIVE FLEET, Jul. 2008, at 16, 18 (finding that parking lots are the most common car accident location, representing 25% of accidents overall). See also State of Cal. Dep't of Transp. Div. of Aeronautics, California Airport Land Use Planning Handbook 8-8 (Jan. 2002), available at <http://www.dot.ca.gov/hq/planning/aeronaut/documents/ALUPHComplete-7-02rev.pdf> (finding that only 7% of commercial air accidents take place greater than five miles from an airport).

2. See, e.g., Jennifer L. Bailit & May Hsieh Blanchard, *The Effect of House Staff Working Hours on the Quality of Obstetric and Gynecologic Care*, 103 (4) OBSTETRICS & GYNECOLOGY 613, 615 (April 2004) ("although physicians may be more rested [given more frequent shift changes], the errors associated with the increase in shift changes that occur with shorter shifts may offset the gains to be made from decreasing sleep deprivation.").

3. Drug Price Competition and Patent Term Restoration Act of 1984 (Hatch-Waxman Act), Pub. L. No. 98-417, 98 Stat. 1585 (codified in relevant part at 21 U.S.C. § 355).

Hatch-Waxman is intended to encourage the first generic to launch a so-called “Paragraph IV” challenge to an existing drug on the ground that the patent is invalid or the new entrant does not infringe the patentee’s patent.<sup>5</sup> For the most part, it appears that the generic manufacturers make rational calculations in their decisions on which patents to challenge and when to challenge them, often by going after the weakest link in the valuable patent.<sup>6</sup> But at the same time, there is an evident risk that collusive agreements between the incumbent patent holder and the first generic entry could slow down the entry of other generic manufacturers into the marketplace, thereby creating welfare losses through their market division.<sup>7</sup> The customary account of patent law treats these arrangements as though they are an impediment to social welfare by delaying the time when new generic entry can lower the price of the drug for all persons in question. The same position is taken by Michael Carrier<sup>8</sup> with respect to “product hopping,” the concerted effort of incumbent patentees to shift their customer base over to a new drug in the same class as the drug over which patent protection has expired in whole or in part. The shift from a tablet to capsule is one common strategy. To pass judgment on these issues, it is often necessary to ask the thankless question of whether the supposed advances in science exceed the preclusive effect that arises if the original product is removed from the Orange Book—or official FDA registry of drugs available for sale—in ways that limit competition.<sup>9</sup> One common theme that unites the articles in

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4. See, e.g., C. Scott Hemphill & Bhaven N. Sampat, *When Do Generics Challenge Drug Patents?* (Columbia Law & Econ. Working Paper No. 379, 2010), available at [http://papers.ssrn.com/sol3/papers.cfm?abstract\\_id=1640512](http://papers.ssrn.com/sol3/papers.cfm?abstract_id=1640512).

5. 21 U.S.C. § 355(j)(2)(A)(vii)(IV) (2010).

6. See Hemphill & Sampat, *supra* note 4, at 4 (“Our results provide support for the proposition that generic drug makers opportunistically challenge weaker patents that block entry.”).

7. See, e.g., *In re Cardizem CD Antitrust Litig.*, 332 F.3d 896 (6th Cir. 2003) (holding reverse payment agreements per se illegal); *Valley Drug Co. v. Geneva Pharma., Inc.*, 344 F.3d 1294, 1308 (11th Cir. 2003) (holding those same payments not per se illegal). For a smattering of the scholarship, see Herbert Hovenkamp et al., *Balancing Ease and Accuracy in Assessing Pharmaceutical Exclusion Payments*, 88 MINN. L. REV. 712 (2004); Daniel A. Crane, *Exit Payments in Settlement of Patent Infringement Lawsuits: Antitrust Rules and Economic Implications*, 54 FLA. L. REV. 747 (2002).

8. Michael A. Carrier, *A Real-World Analysis of Pharmaceutical Settlements: The Missing Dimension of Product Hopping*, 62 FLA. L. REV. 1009 (2010).

9. This was the central issue in the so-called TriCor litigation. See Richard Epstein, *The Intersection of Antitrust, Patents, and FDA Law: The TriCor Litigation*, GCP: THE ONLINE MAGAZINE FOR GLOBAL COMPETITION POLICY (Mar. 2009, Release Two) (expressing caution about the general use of monopolization claims under Section 2 of the

this Symposium is their desire to shift the balance of legal power toward the new entrant as against the incumbent.

I think that the drift of the current argument pushes the balance too much in favor of the generic side of the equation. I reach this conclusion in part because my own activity in the pharmaceutical industry—none of which is current—has been on behalf of the research pharmaceutical companies. I am all too well aware of the way in which they have been buffeted by a wide range of developments. To put this discussion about generic entry into larger perspective, it is necessary at the outset to place two additional items on the table. First, it is important to recount at the outset the various developments that have compromised the legal climate for innovation in recent years, leading to what has now become apparent, a decline of both new molecular entities and the level of research and development in the industry on the other, without signs of a near term reversal. The second addresses the relative importance of two kinds of competition. The first is between the patented drug and its generic competitors. The second is between two patented drugs, neither of which has any a generic variants on the market. Once these two points are essayed, it could well turn out that the real risk today lies in the lagging development of new drugs, not in the wider dissemination of those that have gone off patent. If so, then the obvious legal tilt toward generics could calibrate the balance in the wrong way.

## II. Obstacles To New Drugs

There is little dispute today that the rate of drug innovation is falling. The major question has to do with its causes. One issue is, of course, that the past advances in medical technology have taken all the low-hanging fruit. The newer approaches have to deal with more complex conditions that are harder to attack by some single simple maneuver. We are no longer at the stage where innovative dietary changes can stop such vitamin-deficiency diseases as pellagra, beriberi, and scurvy, or even at the stage where the isolation of insulin can put a huge dent in the management of diabetes.<sup>10</sup> We are instead left with complex cancers on the one hand, and difficult to understand

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Sherman Act). The TriCor litigation resulted in a \$184-million settlement. See Shirley S. Wang, *Abbott to Pay \$184 Million in Tricor Suits*, WALL ST. J., Nov. 21, 2008, at B4.

10. For how this played out, see Richard A. Epstein, *The Tale of How Insulin Came to Market*, DEFINING IDEAS: A HOOVER INSTITUTION JOURNAL (Jan. 2, 2011), available at <http://www.hoover.org/publications/defining-ideas/article/61436>.

diseases like autism and Alzheimer's disease, which may depend on complex interactions of multiple biological and environmental factors, on the other. But even after we allow for this steep climb up the cost curve, the changes in the last dozen years or so make it clear that institutional changes that are introduced to "protect" consumers can themselves have serious side effects in terms of reduced innovation.

#### A. FDA Standards for Clinical Trials

Without question, the entire practice of clinical trials has gotten longer and more protracted today than ever before. At every juncture, the FDA insists upon more trials with respect to more possible side effects than it has done in previous years. One recent illustration involves the prescription diet pill Contrave, which the FDA declined to approve as a treatment for obesity because its maker, Orexigen Therapeutics, need to first perform a "long term study" to ensure that the drug does not increase the risk of heart attacks.<sup>11</sup> This decision was not an isolated event, as in previous months the FDA took the same hard stand against two other diet drugs. As a matter of general drug policy, the decision offers troublesome confirmation that the FDA is more concerned about remote future risks than it is about palpable current ones, so much so that one commentator lamented that in the current environment "tap water would not be approved,"<sup>12</sup> doubtless because of its countless impurities.

For these purposes, the key point is that these FDA decisions clearly filter back into antecedent decisions, including the ever-greater need to conduct overseas trials, where it is harder to keep tabs on their operations. At the same time, the costs of running these trials in the United States have increased because of an increased reluctance of people to enter into clinical trials, just at the time when more subjects need to be recruited into them.<sup>13</sup> Accordingly, many ill people seek to avoid the delays of clinical trials by seeking to use any drug that has passed Phase I trials, so long as it is not believed unacceptably toxic to human beings in the quantities they are likely to

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11. See Andrew Pollack, *F.D.A. Fails to Approve Contrave, a New Diet Drug*, N.Y. TIMES Feb. 2, 2011, available at <http://www.nytimes.com/2011/02/02/business/02drug.html>.

12. *Id.* (quoting Morgan Downey, editor of the online Downey Obesity Report).

13. See Carl Elliott, *Guinea-Pigging*, NEW YORKER, Jan. 7, 2007, available at [http://www.newyorker.com/reporting/2008/01/07/080107fa\\_fact\\_elliott](http://www.newyorker.com/reporting/2008/01/07/080107fa_fact_elliott) (detailing the difficulties in filling out clinical trials).

use.<sup>14</sup> The protocols for starting these programs are more complex than before because of the heightened level of activity by Institutional Review Boards that add cost and slow down the rate of development. The number of new drugs that make it through the FDA approval process remains stagnant at best<sup>15</sup> and the percentage of drugs in clinical trials that make it through the FDA approval process has dropped from about 14 percent a decade ago to about 8 percent in more recent years. Clearly, this rate of return does not go unnoticed by drug companies, who have to be more selective in their research agendas. Research budgets have already contracted in light of the new realities about the probability of drug approvals, from a peak in nominal constant dollars of about \$47 billion in 2007 to about \$44 billion today.<sup>16</sup>

Those changes are reflected in particular disease areas. Right now there is a vast increase in the frequency and intensity of diabetes. Yet recently, four major companies have terminated their research programs because they cannot cope with the ever-higher demand in clinical trials, which demand huge investments today with reduced chances of approval and success years down the road.<sup>17</sup> One reason for this shift in emphasis has been the manifest alteration in the operation of the Prescription Drug User Fee Act,<sup>18</sup> which goes through multiple alterations, as it is reauthorized on a five-year cycle (with the added effect of introducing other collateral changes in practice). In its original inception, the program allowed pharmaceutical companies to make direct contributions to the FDA so that it could hasten the approval process for potentially high rate returns. In its early years, PDUFA appears to have done just that, notwithstanding the peculiar situation in which the companies supply

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14. For an expression of those concerns, see *Abigail Alliance for Better Access to Dev. Drugs v. von Eschenbach*, 495 F.3d 695 (D.C. Cir. 2007) (en banc).

15. Jennifer Corbett Dooren, *Drug Approvals Slipped in 2010: Some Potential Blockbusters Suffered Delays Amid FDA's Tougher Safety Stance*, WALL ST. J., Dec. 31, 2010, available at <http://online.wsj.com/article/SB10001424052748704543004576052170335871018.html>.

16. Gardiner Harris, *Federal Research Center Will Help Develop Medicines*, N.Y. TIMES, Jan. 23, 2011, available at <http://www.nytimes.com/2011/01/23/health/policy/23drug.html>.

17. See T.R. Franson, *Has the FDA Amendments Act of 2007 Impaired Drug Development?*, CLINICAL PHARMACOLOGY & THERAPEUTICS, Feb. 2011, at 169, available at <http://www.nature.com/clpt/journal/v89/n2/pdf/clpt2010301a.pdf>.

18. Prescription Drug User Fee Act of 1992, Pub. L. No. 102-571, 106 Stat. 4491 (1992) (codified as amended in scattered sections of 21 U.S.C.).

the FDA with funding for the approval process of their own drugs.<sup>19</sup> Thus, as approval times shortened, the quality of the approvals remained constant, resulting in gains for both consumers and producers that far exceed the sums invested by the company.<sup>20</sup> But in its most recent iteration in 2007, the entire focus of the program has changed, as a greater fraction of PDUFA revenues have been devoted to *ex post* surveillance, including the creation of risk evaluation mitigation strategies, or REMS, whose broad scale implementation has left far less money in the till for PDUFA's original mission. Any alteration in the interface between branded and generic drugs can only aggravate this difficulty.

### **B. Patent Standards**

The second set of obstacles arises in connection with the patent system. One issue arises with the assistance that the Hatch-Waxman Act provides for the producers of new drugs. The purpose of the Act is to allow for periods of up to five years to offset the time that the new drugs languished in clinical trials without proof of sales. As clinical trials get longer, the effective terms of patents, i.e., the years that they are available for sale, get shorter. That development both delays the entry of the new drug to market and reduces the number of years of marketing exclusivity. The losses in those out-years are often substantial, as patent drugs typically pick up market share in their last years of life.

In addition, it seems to be more likely now that patent challenges will be successful on a variety of grounds, which again reduce the incentives for innovation.<sup>21</sup> The point here is not that all these challenges are inappropriate, for clearly a system as imperfect as the American patent system is capable of issuing patents that should be properly denied. But it is the rising level and frequency of successful challenges that is the source of concern. Higher rates of invalidation lead to lower rates of innovation, all other things being held equal.

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19. This process has been repeatedly attacked on abstract grounds by individuals who typically do not trouble themselves with the evidence on the ground. See, e.g., MARCIA ANGELL, *THE TRUTH ABOUT THE DRUG COMPANIES: HOW THEY DECEIVE US AND WHAT TO DO ABOUT IT* 208 (2004).

20. See Tomas Philipson et al., *Cost-Benefit Analysis of the FDA: The Case of the Prescription Drug User Fee Acts*, 92 J. PUB. ECON. 1306 (2008).

21. See Hemphill & Sampat, *supra* note 4, at 2.

### C. Pricing

The third set of difficulties with the patent system involves the attacks on its basic pricing structure. Drugs are expensive in the United States relative to their costs in other countries, where state monopsonists can often bargain down the prices for the benefit of local consumers. Yet it is equally clear that no system of marginal cost pricing is sustainable over the long run because it does not allow for any drug company to recover the high fixed costs needed to get the first pill into the marketplace.<sup>22</sup> Yet the constant pressure to allow for the re-importation of drugs from overseas and to increase the level of government purchases at restricted rates through Medicaid all cast a pall over the basic pricing structure, which again translates into lower levels of innovation.

### D. Tort Liability

The fourth set of difficulties with the patent system relates to possible exposures to tort liability. Right now, the movement in the case law is strongly toward the position that the preemption defense cannot be raised on grounds of conflict, field occupation, or frustration of the Congressional purposes.<sup>23</sup> I am comfortable with all three of these defenses on the ground that with respect to standardized products, an *ex ante* set of uniform warnings should be used to supply all the needed information to consumers, while blocking the enormous exposure to tort liability that necessarily hampers innovation. I think that the tough approach on preemption is needed because right now the tendency inside the FDA is, as noted above, to be unduly risk averse. Too few products make it to market, and for them the FDA warnings are often too strong. It is wrong, therefore, to create a global impression that somehow the FDA has fallen down on the job so that tort suits, brought years after the release of the drug, become the offset for FDA inefficiency.<sup>24</sup> All too

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22. See John F. Duffy, *The Marginal Cost Controversy in Intellectual Property*, 71 U. CHI. L. REV. 37, 40–41 (2004). See also *In re Brand Name Prescription Drugs Antitrust Litigation*, 186 F.3d 781, 784–85 (7th Cir. 1999) (explaining price discrimination by prescription drug manufacturers).

23. For the basic framework, see *Rice v. Santa Fe Elevator Corp.*, 331 U.S. 218 (1947), which I severely criticize in Richard A. Epstein, *What Tort Theory Tells Us About Federal Preemption: The Tragic Saga of Wyeth v. Levine*, 65 N.Y.U. ANN. SURV. AM. L. 485, 487–88 (2010).

24. For that view, see David A. Kessler & David C. Vladeck, *A Critical Examination of the FDA's Efforts to Preempt Failure-to-Warn Claims*, 96 GEO. L.J. 461 (2008); for my

often, the opposite is likely to happen, whereby harsh tort judgments by juries moved by the plight of individual plaintiffs only reinforce the negative environment in which new pharmaceuticals are developed and brought to market.

### III. Interbrand Competition

These developments require placing the issue of generic entry in a larger institutional context. The simple inquiry is this: the efforts today to boost the position of generic drugs in the marketplace come at an implicit price that it is all too easy to overlook. The increase in generic/branded competition over some particular drug comes at the cost of an expected reduction in competition between different branded drugs used to treat the same condition. In some cases, the new drug that does not get developed is in the same class as the ones that have just gone generic. That is surely the situation with the market for diet drugs, which has not seen a new entry since Xenical in 1999, which is now little used.<sup>25</sup> The decision to let a new drug on the market has two desirable effects. First, it increases the options for treatment that are available on the market *today*, even before a patented drug goes into its generic state, which could be years away. So we get more competition sooner. Second, the new entrant may well prove to be more desirable for some users in a given class than the current incumbent. Accordingly, the new entrant increases the class of individuals who are benefited by the second entry.

The FDA seems systematically to underestimate the benefits from product diversification and underestimate the costs of delaying new entry. In general, it assumes that all product users are pretty much alike. But that need not be the case, and there could well be some small group of individuals that could benefit from the new product that does not do very well on some established treatments. To be sure, there is no certainty in any of this, but it should be stressed that any decision by the FDA to let some new drug on the market does not mean that someone will choose to use it, or that patients will make any life-or-death decision on the use of a new or dangerous drug without professional assistance, usually by physicians whose precise knowledge of the facts and circumstances of a given case puts them in a far better position to make these individuated

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futile response to their article, see Richard A. Epstein, *The Case for Field Preemption of State Laws in Drug Cases*, 103 NW. U. L. REV. 463, 468–73 (2009).

25. See Pollack, *supra* note 11.

judgments than the FDA, which of necessity only operates on the strength of averages.

Nor is it possible to overlook the even larger effects of delay with respect to those drugs that do, on a belated basis, make it onto the market at which point they become the dominant drug. Finding estimates of these figures is not easy to do but an instructive study by Tomas Philipson and his coauthors

... find[s] that PDUFA raised the private surplus of producers, and thus innovative returns, by about \$7 to \$11 billion. Depending on assumptions about the market power of producers during patent protection, [they found] that PDUFA raised consumer welfare between \$7 and \$20 billion; thus the combined social surplus was raised by \$14 to \$31 billion.<sup>26</sup>

Those impressive numbers arise in connection with a study that examines how a reduction under PDUFA leads to reduction in approval times by at most several months. But the entire structure of clinical trials prior to the submission of a new drug application is today far more drawn out than that, for PDUFA does nothing at all to change the various norms that govern clinical trials prior to the submission of a final application, which is where the vast amount of the delay takes place. We get a *lower bound* estimate of these potential gains from new entry by looking at those drugs that do make it onto the market, by determining both its effectiveness in the population that it serves and the years of delay before entrance takes place. But the correct estimation of the losses from tardy clinical trials has to make two further adjustments. The first of these is to guess the number of clinical trials that were either stopped or never attempted in anticipation of the gauntlet that they would be required to run. The second is to estimate the dangers from letting bad drugs on the market that then have to be subsequently removed. Philipson and his colleagues seek to get a handle on this number by asking about the number of individuals who have been harmed by products that were eventually taken off the market because of some defect, only to find that this number is small relative to the lives saved from earlier entry onto the market, even if it could be assumed that all product withdrawals were related to some defect in the PDUFA process, a manifestly conservative assumption. Their estimate of lives saved from getting drugs more quickly to market runs from between

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26. See Philipson et al., *supra* note 20.

140,000 and 310,000 life years.<sup>27</sup> The extreme estimate of the lives put at risk tops out at 56,000 life years lost. From an ex ante perspective, people behind the veil of ignorance surely do better by a decision to take prudent risks.

The basic point is reinforced looking at the situation with COX-2 inhibitors, where the removal of Vioxx from the marketplace in September 2004 made Celebrex the dominant player in the market.<sup>28</sup> Yet some patients will do better under the former drug than the latter; and it could well be that some alternation between two drugs could be superior to a steady diet of the one. In addition, there could be specialized uses, such as the control of bleeding after surgery, in which Vioxx outperforms Celebrex. For these purposes, it does not matter that we are talking about removing an existing drug from the market, instead of adding a new one. Either way, the contraction of the patient's choice set comes at a very high price, for if downstream users are in general best able to decide which drug is more effective in given settings, the irreversible decision of FDA forces many people to settle for second best. For these purposes, it hardly matters whether the loss in private choice stems from an underprotective patent system or from an overzealous FDA.

The positive effects of new entry are likely to be more dramatic if the new entrant comes from a previously undeveloped class of new drugs, which opens up some alternative pathways to treatment. At this point, the high price for the new drug has to be put into perspective. The amount of money that people can pay for a drug is strictly limited by their net worth. The amount of benefit that they can obtain from a drug is often measured by increased longevity and quality of life, which could be far greater than this willingness-to-pay measure. It is therefore incumbent on the legal system to take steps to make sure that these new entries take place. The constant sniping at the abuse of the six month co-exclusivity period, or the attacks on "product hopping" through the use of multiple patents of different strength on a given product thus have to be put in the perspective of knowing the second-best situation that exists in the new drug market. Improvement on that margin has to be measured against the decline of new entry.

How this is to be done is hard to estimate in the abstract. In order to get traction on this issue, it is critical to develop some data

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27. *Id.*

28. For my account, see RICHARD A. EPSTEIN, OVERDOSE: HOW EXCESSIVE REGULATION STIFLES PHARMACEUTICAL INNOVATION 132 (2006).

on questions that are insufficiently explored: how long do generic drugs remain on the market? The issue here is complex because one social advantage to branded drugs is that single ownership leads to extensive advertisement which can get the drug into the hands of high demanders. Generic drugs tend to be less promoted, and it is an open question whether the knowledge of their desirable properties in the hands of HMO offer sufficient offset for the loss of marketing efforts. That question in turn may well depend on whether a competition between a first generation generic and a second generic patented drug will come out in favor of the former even in the face of substantial price differentials in favor of the generic drug. Clearly there is no necessary answer to any of these questions. But the very uncertainty about the underlying choice is reason enough to be cautious about any fresh efforts to advantage the generic drugs at the expense of their branded rivals. And the ultimate irony may well be this: the next generation of generic drugs is the current generation of patented drugs. Let the spigot shut too tightly and both sides of the market could suffer.

#### **IV. Conclusion: What Next?**

It is difficult to know the proper way for patent law to respond to the clear breakdown in the overall drug approval system. My own preference is to increase the Hatch-Waxman offsets so that it is possible to obtain one year of additional patent protection for each year that an approved patented drug languishes in clinical trials. At this point, the FDA may sense that its own decisions will have real impact on the switch from branded to generic drug status, which could perhaps induce it to expedite its hearings in order to capture some of the benefits hinted at by the PDUFA studies of Philipson and his colleagues. The needed extension would be as much as four or five more years for many blockbuster drugs, which is worth billions of dollars more than the six month extensions that have been associated with the coexclusivity period. But if the gain from their use is as large as I suspect it is, this fundamental reform should cast a new light on the various coexclusivity deals. In my own view, I have cautiously come to think that the law ought to take this position. Let the incumbent and the first entrant divide the market between them in whatever way they see fit. In the end we should expect them to seek to maximize their joint product by choosing the same prices and quantities as the single incumbent had done before the patent was invalidated. Taking this position therefore has two advantages. First,

it simplifies what is now a complex and inconclusive inquiry as to which of these arrangements pass the rule of reason test and which of them do not. Second it probably corrects the current imbalance in the system, stemming from the short period of exclusivity left under the current regime. At worst, therefore, this maneuver looks like an extra six months on the patent life, which is welcome in its own right. The gains from additional stimulation today could easily offset the monopolization effects down the road. Put otherwise, this approach makes best in the second best world by addressing the more fundamental flaw in the patent system: too-short initial terms.