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Orange Book patent listing: The rationale and economic impact of the new rule

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Mark Pohl

Abstract Listing a patent in the US Food and Drug Administration’s (FDA) ‘Orange Book’ of approved pharmaceuticals brings some significant advantages to the patent owner. The FDA has recently changed its requirements for listing patents in the Orange Book. The rule’s significant economic impact creates a unique opportunity to build valuable new pharmaceutical product lines. In this paper, the rationale for the new rule will be reviewed and its significant economic impact — expected, over the next decade, to add $19bn in revenues to generic drug manufacturers and to take away $52bn in innovator manufacturer revenues — measured. Moreover, the legal advantages of listing patents in the Orange Book, potential obstacles to listing a patent and the way in which the rule applies to patents on polymorphic forms of approved therapeutic products will be examined.

Keywords: Orange Book, ANDA, pharmaceutical patent, drug patent, pharmaceutical economics, polymorph patent

THE BROAD OUTLINE OF THE NEW RULE

The Drug Price Competition and Patent Term Restoration Act of 1984 (the ‘Hatch–Waxman Act’) balances conflicting interests: promoting lower-price generic product competition to high-priced innovator drugs, while encouraging investment in the pharmaceutical research needed to discover the innovator drugs of tomorrow. The Act promotes low-price generic product competition by creating a process to both expedite the filing and approval of generic drug applications and to resolve the innovator drug’s patent status before the generic product is marketed. At the same time, the Act encourages investment in research by protecting the patent interests of the patent owner and innovator drug company.

As part of the Hatch–Waxman Act, the US Food and Drug Administration (FDA) recently enacted new rules controlling the listing of drug patents in the FDA’s ‘Orange Book’ of approved pharmaceuticals.¹ The new rule balances the innovator companies’ intellectual property rights against the public’s desire to get generic drugs onto the market in a timely fashion. The new rule says that an innovator will be entitled to only one automatic 30-month stay regardless of the number of patents listed in the Orange Book. Eliminating multiple 30-month stays is expected to speed up the approval and market entry of generic drugs.

The new rule also clarifies patent submission and listing requirements. Specifically, patents claiming a different polymorphic form of the active ingredient described in the new drug application

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(NDA)\(^2\) must be submitted if — and only if — the NDA holder has test data demonstrating that a drug product containing the polymorph will perform in the same way as the drug product described in the NDA.

The new rule, thus, *inter alia*:

- allows only one 30-month stay\(^3\) per abbreviated new drug application (ANDA) or §505 (b)(2) application
- requires the submission of certain patents claiming a different polymorphic form of the active ingredient described in the NDA
- adds a requirement that, for submission of polymorph patents, the NDA holder must have test data demonstrating that a drug product containing the polymorph is ‘bioequivalent’ to the innovator drug product.

One can glean an understanding of the new rule by reading it; a complete copy of the rule is available online at www.LicensingLaw.net/library.asp. Two things that are not clear from the text of the rule, however, are its economic impact on the pharmaceutical industry and the mechanics of how polymorph patents are treated. These two topics each deserve discussion.

**THE SIGNIFICANT IMPACT OF THE RULE ON PHARMACEUTICAL INDUSTRY ECONOMICS**

**Summary**
The primary economic impact of this rule is a transfer of wealth from innovator drug firms to generic drug firms and to consumers. The increase in revenues to generics drug manufacturers is estimated to be $19bn over ten years, with innovator firms losing $52bn over the same period.\(^4\)

The economic impact arises primarily from the elimination of multiple 30-month stays, which is expected to result in earlier market entry by generic drug manufacturers, without appreciable negative effects on pharmaceutical innovation. Earlier generics competition will result in gains for two groups; it will reduce pharmaceutical prices to consumers and increase net revenues of generic drug manufacturers.

Earlier competition will also result in a revenue loss for innovator drug companies, which loss will be offset slightly by a reduction in associated costs. As a minor note, the rule is also expected to reduce legal fees, yet increase the cost of completing revised patent declaration forms. Finally, those NDA holders wishing to submit patents claiming different polymorphs of the active ingredient described in the NDA will need to have test data demonstrating ‘sameness’.\(^5\)

The financial estimates of the costs and benefits to innovators and generic drugs firms are premised on a few simple concepts.\(^6\) First, the introduction of generic products has little effect on innovator prices.\(^7\) Generic products, by contrast, are generally priced at a fraction of the price of the innovator product, and this fraction decreases over time as more and more generic products enter the market.\(^8\) This is shown in Table 1.

Based on the lower prices afforded by generics, the percentage of the market supplied by generics increases over time.

**Table 1: Generic products rapidly take market share from innovators**

<table>
<thead>
<tr>
<th>Months from generic launch date</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic market share (%)</td>
<td>40</td>
<td>40</td>
<td>55</td>
<td>55</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Innovator share (%)</td>
<td>60</td>
<td>60</td>
<td>45</td>
<td>45</td>
<td>30</td>
<td>30</td>
<td>30</td>
<td>30</td>
</tr>
</tbody>
</table>
Table 2: Innovator price holds steady in the face of falling generic prices

<table>
<thead>
<tr>
<th></th>
<th>Months from generic launch date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Generic price (%) of innovator</td>
<td>100</td>
</tr>
<tr>
<td>Innovator price (%)</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 3: Economic effects of the rule (all amounts in units of $1m)

<table>
<thead>
<tr>
<th></th>
<th>2003-04 amount</th>
<th>10-year total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Savings to consumers</td>
<td>3,290</td>
<td>34,822</td>
</tr>
<tr>
<td>Net revenues to generics mfgs</td>
<td>1,810</td>
<td>19,117</td>
</tr>
<tr>
<td>Reduced legal costs to mfgs</td>
<td>de minimus</td>
<td>de minimus</td>
</tr>
<tr>
<td>Revenue loss to innovator mfgs</td>
<td>(4,870)</td>
<td>(51,584)</td>
</tr>
<tr>
<td>Polymorph patent submission fees</td>
<td>(&gt; 10)</td>
<td>(&gt; 90)</td>
</tr>
</tbody>
</table>

The FDA estimates that the innovator’s market share decreases to 60 per cent of the total in the first year, and then gradually down to 30 per cent of the total market within 24 months of the generic product launch. This estimate may in reality be far too kind to the innovator, seriously underestimating both the rapidity and the severity of the innovator product’s market share loss — thus seriously underestimating the present value of the revenue loss to the innovator manufacturer. Nonetheless, these estimates are used here (see Table 2).

One can apply these assumptions for relative price levels and relative market shares (and thus sales volumes) to the pharmaceutical industry’s currently-patented products to calculate aggregate industry-wide dollar amounts at stake. These overall effects and overall net benefits are summarised in Table 3. In calculating this Table, periodic benefits and costs are annualised at a 7 per cent discount rate over ten years, to discount them to a net present value. A ten-year projected period was chosen because the Centers for Medicare and Medicaid Services (CMS), the source of the most reliable US pharmaceutical expenditure estimates, project these expenditures only for the next ten years. One can, however, expect the rule to generate substantial effects beyond this time period.

The increase in revenues to generic drug manufacturers is estimated to be $19.117bn over ten years, or $1.8bn per year if annualised assuming a 7 per cent discount rate. The benefit to consumers is estimated to be $34.822bn over ten years, or an annualised $3.3bn. The reduction in revenues to innovator firms is mitigated somewhat by the reduction in marketing expenses and the fact that the cost would be $51.508bn over ten years, or an annualised $4.9bn. The ten-year net benefit is $2.356bn, and the annualised net benefit is approximately $220m.

As innovator drug firms face a decline in revenues, they will save on substantial resources used to support their products. These support costs, which include marketing, advertising and administration, outweigh the costs associated with polymorph testing and completing the revised declaration. These support costs are based on a point estimate provided by literature that does not customarily provide confidence intervals.

Gains to the generic drugs industry

There are two principal effects of the elimination of multiple 30-month stays.
Generic drug manufacturers gain the market share from innovators. Generics revenues, therefore, would be expected to increase.

The first-year estimates are escalated by the CMS-projected annual percentage increases in prescription drug expenditures to obtain estimates for ten years. This ten-year stream is then annualised at a 7 per cent discount rate to obtain the annualised estimate.

Innovator market share erosion is accompanied by a gain in generics market share. The US government estimates the first-year increase in generics firms’ revenues to be $1.120bn. Escalating this impact by the annual increases in pharmaceutical expenditures yields a ten-year revenue gain of $19.117bn. The annualised impact using a 7 per cent discount rate is $1.805bn.

By addressing multiple 30-month stays, the new rule removes a barrier to entry for generic drugs firms. In principle, the removal of a barrier to entry would imply an increase in economic efficiency. There is no significant increase in the quantity of drugs demanded with generics entry; this implies no gain in efficiency from the removal of the barrier to entry. Nevertheless, this rule encourages more frequent and earlier market entry by generic drug firms; to this extent, this rule has the potential to increase economic efficiency.

The costs of allocating legal resources to defending patents are substantial. Eliminating multiple 30-month stays per ANDA and §505 (b)(2) application reduces the number of instances where innovator and generic drug firms would engage in such litigation. Moreover, this rule may reduce litigation to the extent that it reduces incentives for submitting patents which do not qualify for additional 30-month stays. The reduction in resources devoted to litigation should result in savings to both innovator and generic drugs firms.

The total quantified benefits of this new rule include the gains in generic drug manufacturer revenues and consumer savings from earlier access to less expensive pharmaceuticals. These quantified gains to consumers and generic drug companies are the result of an economic transfer. The first-year benefits to generic drugs manufacturers and consumers are $1.119bn and $2.040bn, respectively. Escalating these base year costs over ten years yields generic drug manufacturer revenue gains of $19.117bn and consumer savings of $34.822bn, for a total of $53.940bn. The ten-year annualised benefits, using a 7 per cent discount rate, are $1.805bn for generic drug manufacturers and $3.288bn for consumers, for a total of $5.093bn.

**Losses by innovator firms**

The rule precipitates two kinds of economic ‘costs’: innovators lose revenues from earlier generics competition and must complete patent declarations. The loss in revenues to innovator drug companies is part of an economic transfer. In addition, there is a burden to industry from the requirement that, for submission of patents claiming different polymorphs of the active ingredient described in the NDA, there must be test data demonstrating that any drug product containing a polymorph is bioequivalent to the drug product described in the NDA.

While the first 30-month stay obtained by the innovator is part of the balance struck in the Hatch-Waxman Amendments to reward innovation, subsequent stays are not part of this balance. According to the Federal Trade Commission (FTC) report, most of the court rulings examined by the FTC, which involved a subsequent 30-month stay, found the underlying patent to be either invalid or not infringed.

The elimination of multiple 30-month stays per ANDA or §505 (b)(2) application allows generic drugs to enter the market earlier. Upon entry, prices of subsequent generic versions of an innovator drug gradually decline, and the generics take market share from the innovator. With the loss of market share, innovator revenues are
lower than they would have been had the innovator been allowed to use multiple 30-month stays to delay generics entry. Using data from instances where generics have been blocked with multiple 30-month stays enables one to calculate the impact of a typical drug being blocked for a typical period of time. The loss in innovator revenues during the first year that the new rule is effective is estimated to be $3.160bn. This may be mitigated somewhat by a reduction in innovators' costs; with earlier generics competition, innovators may reduce marketing expenses. This estimated reduction in support costs is estimated to be approximately $142m in the first year. Thus, the new effect in the first year — after adjusting to reduce support costs — is a $3.017bn revenue loss.

The total costs of the new rule include the revenues lost to innovator firms from the erosion of market share (mitigated by the decrease in support costs), the cost of completing a more detailed patent declaration and the costs associated with the requirement that test data exist demonstrating 'sameness' in order to submit a polymorph patent for listing. The estimated one-year loss in revenues from erosion of market share is $3.160bn, the reduction in support costs would reduce this loss by $142m. The cost of providing the patent declaration information is only $293,000, and the cost associated with bioequivalence testing for polymorph patents is $3.3m. Thus, the overall cost to innovator firms is about $3.022bn during the first year.

In projecting the future, one must account for changes in the market for pharmaceuticals. The Office of the Actuary at the CMS projects that expenditures on prescription pharmaceuticals will increase dramatically in the near future. The projected growth in pharmaceutical expenditures is factored in by escalating the one-year estimate by the annual CMS-projected growth in prescription drug expenditures. The estimated ten-year cost for the new rule is thus $51.584bn. Annualisation over the ten-year period at a 7 per cent discount rate yields a present value loss to innovator firms of $4.871bn per year.

It is clear that the new rule has a significant impact on the economics of the pharmaceutical industry. One area in which the new rule creates an opportunity is with polymorphic forms of approved pharmaceutical ingredients. The next section reviews the new procedure for listing patents on polymorphic forms of drug products.

POLYMORPH PATENTS UNDER THE NEW RULE
Drug substances that are the same active ingredient, but that are in different physical forms, are often called 'polymorphs'. For example, a given molten chemical may be cooled down until it crystallises; depending on the rate of cooling or other factors, the molten chemical might crystallise in any of a variety of specific configurations. While the specific crystalline configurations differ, the chemical compound remains the same; thus, the different crystalline forms of the one compound are sometimes known collectively as 'polymorphs'.

While made of the same chemical compound, the various polymorphs might have different shelf-life stability, solubility or other characteristics, which may prove advantageous or disadvantageous in manufacturing, formulating or administering the specific active ingredient compound. Thus, one or another specific polymorph might prove unusually valuable.

A pharmaceutical manufacturer may obtain a patent on an active pharmaceutical ingredient in general, and then obtain any number of follow-on patents on various polymorphic forms of that ingredient. In the past, certain pharmaceutical manufacturers would do so, listing numerous follow-on polymorph patents in the Orange Book — and then asking for separate 30-month stays for each follow-on patent.
The new rule attempts to curtail this practice. It says that the applicant 'shall submit information only on those patents that claim the form of the drug substance that is the subject of the pending or approved application or that claim a drug substance that is the same as the active ingredient that is the subject of the approved or pending application'. An NDA applicant or holder determines whether the drug substance is the 'same' by considering whether the drug substances can be expected to perform the same with respect to such characteristics as dissolution, solubility, and bioavailability' (i.e. bioequivalence parameters).

Under the rule, an NDA applicant or holder is required to submit a patent claiming a different polymorph from that of the drug substance described in the NDA, if a drug product containing the polymorph is shown to be bioequivalent — i.e. performs the same as the drug product described in the NDA with respect to dissolution, solubility and bioavailability. The rule thus makes the Orange Book standards generally consistent with the ANDA approval standards. For ANDA approval purposes, the active ingredient in a generic drug product can be the 'same' as that in the reference listed drug, notwithstanding differences in the physical forms of their active ingredient if the drug product performs the same. Thus, it is consistent to interpret 'drug substance' for patent submission and listing purposes as including certain drug substances having different physical forms if they are to be considered the same active ingredient for ANDA approval purposes.

The rule says that patents that claim different polymorphs of the active ingredient described in the NDA must be listed if — and only if — the NDA applicant or holder is able to establish that a polymorph claimed in a patent is the 'same' active ingredient (i.e. that a drug product containing the polymorph will perform the same as the drug product described in the NDA with respect to such characteristics as dissolution, solubility and bioavailability), and the NDA applicant or holder must submit the patent for listing.

The FDA believes that it is appropriate to have a consistent interpretation of the 'sameness' principle in the patent listing and ANDA approval contexts. Accordingly, the FDA treats polymorphs similarly for Orange Book submission and for ANDA approval.

The submitted patents must claim the 'same' active ingredient as that described in the NDA. A polymorph patent must claim the drug substance (active ingredient) to meet the statutory requirements for submission. The declaration form helps to ensure that the NDA applicant or holder or patent owner confirms that the patent does claim the 'same' active ingredient. The declaration form requires that the NDA applicant or holder or patent owner certifies that test data exist to demonstrate that a drug product containing the polymorph will perform the same as the drug product described in the NDA. If a patent claims more than one polymorph, each polymorph for which the required test data are available must be identified by claim or description in the declaration forms.

The new rule does not require these tests to be submitted to the FDA at the time of patent submission, nor does it require the NDA applicant or holder to conduct the tests itself. The testing requirements, however, ensure that only relevant polymorphs are submitted for listing.

Whether two polymorphs comprise the 'same' active ingredient for the purposes of drug approval is a scientific determination based upon the specific characteristics of the forms of the drug substance involved. Only with testing can the scientific determination be made that the drug product containing the polymorph will perform the same as the drug product described in the NDA. The test data that the NDA applicant or holder or patent owner must certify exist at the time of patent submission are similar to the
type of information required under 21 CFR 314.50 and 21 CFR 314.94.

The required tests or data that would support the statement in the declaration form include the following bioequivalence test data:

- A full description of the polymorphic form of the drug substance, including its physical and chemical characteristics and stability; the method of synthesis (or isolation) and purification of the drug substance; the process controls used during manufacture and packaging; and such specifications and analytical methods as are necessary to assure the identity, strength, quality and purity of the polymorphic form of the drug substance;
- The executed batch record for a drug product containing the polymorphic form of the drug substance and documentation that the batch was manufactured under current good manufacturing practice requirements;
- Demonstration of bioequivalence between the executed batch of the drug product that contains the polymorphic form of the drug substance and the drug product as described in the NDA;
- A list of all components used in the manufacture of the drug product containing the polymorphic form and a statement of the composition of the drug product; a statement of the specifications and analytical methods for each component; a description of the manufacturing and packaging procedures and in-process controls for the drug product; such specifications and analytical methods as are necessary to assure the identity, strength, quality, purity and bioavailability of the drug product, including release and stability data complying with the approved product specifications to demonstrate pharmaceutical equivalence and comparable product stability; and
- Comparative in vitro dissolution testing on 12 dosage units each of the executed test batch and the NDA product.

This test data requirement corresponds to the test data required of ANDA applicants to demonstrate that the drug product containing the polymorph described in the ANDA will perform the same as the drug product described in the NDA. In addition to the data requirements described in sections 314.50 and 314.94, additional information on bioequivalence data is available in the FDA’s Guidance for industry: Changes to an approved NDA or ANDA (November 1999) and Guidance for industry: Immediate release solid oral dosage forms CMS 5 (November 1995).

The stringency of these requirements regarding ‘sameness’ should also address the concerns that the submission of polymorph patents might lead to submission of other patents claiming components which are not, but might be, included in a drug described in an NDA. Given the narrow legal and scientific basis for submission of polymorph patents, the new rule ostensibly does not allow submission of any patents claiming formulations or inactive ingredients not contained in the drug product described in the NDA.

Cost of submitting polymorph patents
The FDA now requires the submission of patent information for patents that claim different polymorphs of the active ingredient described in the NDA. NDA holders will now be able to submit these polymorph patents for listing in the Orange Book, as long as they have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA.

The costs of bioequivalence testing can vary substantially depending on the substance being tested, the number of subjects required, the cost of raw materials.
and other factors. As part of an unrelated study in 1998, the Eastern Research Group (ERG) estimated the cost of bioequivalence testing. The cost of demonstrating that the drug product containing the polymorph will perform the same as the drug product described in the NDA is similar to the cost of demonstrating bioequivalence. Including the cost of manufacturing the batch and the cost of conducting the bioequivalence testing, the ERG found the total cost of performing such bioequivalence testing to be between $70,000 and $750,000. The cost of showing ‘sameness’ is at the higher end of this range, estimated at between $500,000 and $750,000 (in 1998 dollars, not adjusted for inflation).

A firm’s decision to submit a polymorph patent for listing will depend on whether the expected economic benefits to the firm from listing exceed the costs of showing ‘sameness’. The potential benefits from listing polymorph patents may be reduced by the elimination by the new rule, of multiple 30-month stays in approval of ANDA or §505 (b)(2) applications. Thus, the cost of demonstrating ‘sameness’ will, one would expect, deter the submission of low-value patents (patents worth less than the cost to do the requisite bioequivalence testing). One could expect many polymorph patents to be substantially less valuable than the cost to submit the patent for listing, as many patents have little value without the ability to delay generic entry through multiple 30-month stays. The FDA assumes such low-value patents to be worth approximately 20 per cent, or $125,000, of the cost of showing ‘sameness’. By contrast, a polymorph patent with a high potential value (greater than $625,000 — the midpoint of the testing cost estimates) would be viable for listing.

CONCLUSIONS AND RECOMMENDATIONS
The new rule provides for only one 30-month stay per NDA. Thus, it might appear that there is little incentive to list multiple patents such as follow-on polymorph patents. While the value of follow-on patents might be redundant in the near term, in the long term they might prove quite beneficial. For example, listing a polymorph patent might provide somewhat redundant protection while the compound patent remains in force, but when the compound patent expires, the listed polymorph patent may remain as an in-force patent eligible for a 30-month stay in the future. Thus, pursuing and listing a variety of patents remains the most reasonable strategy.

References and notes
1. The orange colour was selected because the list was apparently first published just before the American holiday of Halloween; one of the traditional theme colours for Halloween is orange.
2. In the USA, a new drug may legally be sold only after the FDA concludes that the drug is safe and effective. A new drug’s manufacturer presents clinical data regarding safety and effectiveness to the FDA in an NDA. When a generics company wants to make and market the same drug, this company need not repeat the expensive clinical testing required for an NDA; rather it need only show that its own product is biologically equivalent to the original manufacturer’s product. The generics company presents such bioequivalence data to the FDA in an ANDA. If a generics company wants to make and market a drug that is functionally equivalent, yet somewhat different chemically, it then needs only to show that its product is functionally equivalent to the original manufacturer’s product pursuant to a §505 (b)(2) application.
3. More precisely, the 30-month period may be shortened or lengthened by court order or a court decision regarding the listed patent(s).
5. 21 CFR 314.53(b).

10. Gains and losses include impacts of an economic transfer in addition to changes in resource costs.

11. These estimates are derived using methods and data similar to those described in 68 Fed. Reg. 65448.

