

A day late and a few million dollars short

Dianna Goldenson

The pitfalls of seeking and obtaining a patent term extension.

It's Monday, and your homework assignment is due "within two days." When do you have to hand it in—Wednesday? Or maybe Tuesday? Missing a deadline in school could be a problem but would not ordinarily cost money. In the world of patented drugs, however, missing a deadline could cost millions, even billions, of sales dollars.

At the US Patent and Trademark Office (USPTO), a tricky filing deadline is being frequently miscalculated by applicants for patent term extension (PTE), a procedure that can add up to five years to a patent's life. Until recently, the government was miscalculating this deadline as well, resulting in the grant of several invalid extensions based on late-filed applications. The law is not the problem because the filing period is clearly defined in the statute. The problem is that people are simply counting wrong. Missing the PTE filing deadline is an incurable error, but missing it without getting caught opens a whole other can of worms.

Hatch-Waxman and the value of long-lasting patents

In 2008 alone, total worldwide revenues for the pharmaceutical industry included \$63.7 billion for Johnson & Johnson¹, \$48.3 billion for Pfizer² and \$31.6 billion for AstraZeneca³. Popular branded drugs can bring in several millions of dollars per day before generic competition enters the market. With so much at stake, particularly for blockbuster drugs, brand companies dedicate themselves to maintaining market exclusivity; and they need long-lasting patents on their drug products to do it.

A patent holder has the right to exclude others from making, using, selling or offering to sell the patented invention for a certain

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Table 1 The last 100 applications filed and granted PTE and viewable on the USPTO's online PAIR database

| PTE filing year | No. of applications with miscalculated deadline | No. of applications with correctly calculated deadline |
|-----------------|---|--|
| 2002 | 18 | 6 |
| 2003 | 17 | 9 |
| 2004 | 15 | 0 |
| 2005 | 17 | 4 |
| 2006 | 11 | 2 |
| 2007 | 0 | 1 |
| Total | 78 | 22 |

time period⁴. A patent on a drug becomes most valuable when the drug receives marketing approval from the US Food and Drug Administration (FDA). Because a drug must undergo several years of testing before the FDA approves it, the life of a patent protecting the drug is often ticking away, shortening the duration of patent protection that will be left when the drug reaches the market. To compensate drug developers for some of this lost time, a law was passed as part of the Hatch-Waxman Act that allows a patent to protect the drug beyond its original expiration date, for sometimes as long as five years⁵.

Patents on branded drugs raise barriers that generic drug companies must overcome before they can market their generic versions. For instance, Hatch-Waxman requires brand pharmaceutical companies to list all their patents covering the FDA-approved product (patents that claim the active ingredient, approved formulation and/or approved method of use)⁶ in an FDA publication commonly known as the "Orange Book"⁷. When a company files an Abbreviated New Drug Application (ANDA) seeking approval for a generic drug, it must make an official statement (referred to as a "certification") as to how the marketing of its generic drug will avoid infringing for each patent listed in the Orange Book for the branded drug⁸. Patents listed in the Orange Book can

thus be substantial obstacles, especially if a listed patent was granted an extension and covers the active substance itself. Generic companies often need to wait for such patents to expire before marketing generic versions because it can be difficult to avoid infringement of a so-called "substance patent." The longer the extension, the longer the wait, unless the generic can prevail in costly and protracted patent litigation.

A tricky path To PTE

To obtain a PTE, a patent owner must file an application with the USPTO that satisfies several requirements under 35 USC §156. One of the more innocuous-looking requirements is that the application must be filed in a timely fashion. But many applicants have a hard time identifying the deadline. In fact, not only have many patent lawyers gotten it wrong, but the USPTO and FDA have made this error many times as well.

According to the PTE statute, "an application may only be submitted within the sixty-day period beginning on the date the product received permission under the provision of law under which the applicable regulatory review period occurred for commercial marketing or use"⁹. The statute seems clear enough: FDA approval triggers a 60-day period for filing a PTE application, starting with the approval

date. In the world of federal laws and institutions, however, when a deadline is given, day one of the relevant time period is almost invariably the day after the trigger date. For example, most people would presume that a homework assignment that is given on a Monday and due “within two days” must be handed in by Wednesday. This is the common, well-entrenched convention¹⁰. The PTE statute conflicts with this convention by stating that the 60-day period begins on the date of regulatory approval. Thus, the first day of the filing period is the trigger date. For example, if FDA approval occurs June 15th, the PTE application filing deadline is August 13th. Correctly identifying this deadline is critical. If you miss it, the patent is ineligible for extension.

In the last 100 filed applications that have been granted PTE and are viewable on the USPTO's online PAIR database¹¹, 78 incorrectly identify the 60th day of the filing period¹², as shown in Table 1. The USPTO may have recognized the danger of this miscalculation because its own manual, the *Manual of Patent Examining Procedure* (MPEP), cautions PTE applicants to file early “to avoid the application being denied because the filing deadline was inadvertently missed”¹³.

Near misses, casualties and possible legislative reform

Given the high stakes and draconian consequences, one would expect PTE applicants to file early, and most do. Much of the necessary information can be gathered even before FDA approval, so planning ahead is very helpful as 60 days can lapse quickly during the busy period just after a company receives FDA approval. Yet, this is undoubtedly a dangerous situation, particularly because the 60th day has been regularly miscalculated for over 20 years by the USPTO, the FDA and most patent lawyers who submit these applications. In dozens of cases, PTE applicants have unwittingly filed on the 60th day, evidently thinking that they were filing a day early. This group of lucky applicants includes, for example, the makers of Lovenox (enoxaparin) and Crestor (rosuvastatin calcium). The patent for Lovenox (at one time, the best selling anti-thrombotic drug in the world) was extended by three years,

during which this product brought in an additional \$5.58 billion in global sales. The patent on Crestor (a cholesterol medicine with \$3.6 billion of global sales in 2008) will expire in 2016 after an extension of about 3.5 years. Without this bit of luck, these PTE applicants would have been a day late and a few billion dollars short.

Of course, not all applicants have been this lucky and a number of large drug companies have forfeited their PTE eligibility by missing the filing deadline (Table 2).

One case that achieved notoriety relates to the Angiomax (bivalirudin) PTE application¹⁴, where the USPTO initially miscalculated the deadline¹⁵, but later corrected itself, nevertheless concluding in both instances that the application was late¹⁶. In support of its final decision, the USPTO cited *Unimed, Inc. v. Quigg* as a court decision that addressed the issue of PTE application timeliness and stated that “section 156(d)(1) admits of no other meaning than that the sixty-day period begins on the FDA approval date”¹⁷.

Prompted by the Angiomax case, lawmakers in 2006 tried to amend the PTE statute by proposing a bill dubbed the “Dog Ate My Homework Act”¹⁸. Under this bill, requests for an extension would be allowed a three-day grace period at the discretion of the USPTO director for unintentional delays, which would presumably include delays due to inadvertent miscalculation of the filing deadline¹⁹. This grace period would retroactively apply to requests for PTE that are pending before the USPTO or still subject to judicial review at the time of enactment. But this safety net does not come cheap. For PTE applications on anticoagulant drugs such as Angiomax, the bill would impose a late fee of \$65 million (ref. 19). For other products, the late fee would depend on commercial success, that is, the sum of “any net increase in direct spending arising from the extension of the patent term,” “any net decrease in revenues arising from such patent term extension,” and “any indirect reduction in revenues associated with payment of the fee”²⁰. The proposed bill was first included in the Patent Reform Act of 2007 (HR 5120), but efforts to pass this legislation stalled. The bill was resurrected in the Responsive Government

Act of 2008 (HR 6344), which quickly passed the House of Representatives in June amid strong supporting statements from a few congressmen, one of whom went so far as to say that the bill “would save lives”²¹. The bill was referred to a Senate subcommittee last July but has not been passed as of this writing.

The “Dog Ate My Homework Act” could also benefit the makers of A180 (danofloxacin; an animal drug for treating bovine respiratory disease), Prilosec OTC (omeprazole; a human drug for treating heartburn) and Symbicort (budesonide and formoterol; a human drug for treating asthma), all of which were denied PTE for these products, at least partly owing to a late PTE application.

In the case of A180²², the FDA first concluded (mistakenly) that the application was timely filed²³. Later, the USPTO corrected the FDA's error and concluded that the application was untimely²⁴. In the case of Prilosec OTC²⁵, the FDA again mistook the application as timely²⁶, after which the USPTO sent the FDA a letter correcting this mistake and stating that the PTE application was ineligible on grounds that included untimely filing²⁷. About six months later, in October 2008, the FDA responded to the USPTO with a letter apologizing for its error and agreeing with the USPTO's calculation²⁸. Thus, at least the government is coming up to speed on computing deadlines.

The Prilosec OTC PTE applicant petitioned the USPTO director, alleging that the USPTO's “new” method of calculating the 60-day deadline would cause “unduly prejudicial and detrimental consequences for the Applicant”²⁹. In its petition, the applicant highlighted the extensive confusion surrounding the 60-day deadline and alleged that 13 patents have been granted extensions despite applications being filed after the 60-day deadline, as calculated by the USPTO's method. Although several PTE applications were indeed filed late and then improperly granted, this is a tangled situation that may only spread the grief around rather than resolve it for the Prilosec OTC PTE applicant, especially because the applicant's petition does not address the clear language in the statute stating that the 60-day period begins on the date of regulatory approval. In

Table 2 Drugs that have forfeited their PTE eligibility by missing the filing deadline

| Product name | Applicant | Date of FDA approval | PTE appl. filing date | True deadline | Mistaken party | PTE status |
|--------------|------------|----------------------|-----------------------|----------------|--------------------------------------|---------------------------------|
| Angiomax | NDA holder | Dec. 15, 2000 | Feb. 14, 2001 | Feb. 12, 2001 | Applicant and USPTO (initially) | Denied |
| A180 | Patentee | Sept. 20, 2002 | Nov. 19, 2002 | Nov. 18, 2002 | Applicant, USPTO and FDA (initially) | Denied |
| Prilosec OTC | Patentee | June 20, 2003 | Aug. 19, 2003 | Aug. 18, 2003 | Applicant and FDA (initially) | Denied |
| Symbicort | Patentee | July 21, 2006 | Sept. 19, 2006 | Sept. 18, 2006 | Applicant | Denied, reconsideration pending |

response to this petition, the USPTO issued a “final agency decision” denying PTE based on the same grounds³⁰.

In the Symbicort case³¹, the FDA got it right on the first try and identified the application as untimely³². The USPTO later denied PTE in June 2008 for this and other reasons³³. In its decision, the USPTO expressed surprise at the applicant’s miscalculation, stating, “It is unclear how Applicant, who specifically correctly indicated that the first day of the sixty-day period ‘began on July 21, 2006,’ calculated that the end point of the sixty-day period was any day other than September 18, 2006”³⁴. Hence, the USPTO may still be unaware of the extent of these errors. In its request for reconsideration, the applicant provided essentially the same arguments and supporting information presented in the Prilosec OTC case, but referenced a 14th patent for which a PTE was granted even though the application was filed after 60 days³⁵.

Consequences of improperly granted PTE

As of this writing, at least 13 patents have been improperly extended based on late-filed PTE applications, four of which have not yet expired. Because some PTE applications are not viewable through the PAIR database, it is possible that other granted applications and/or pending applications were untimely, but the USPTO and/or FDA may have failed to spot the errors. A range of issues could arise from such errors, apart from the patent being limited to its original expiration date and thereafter unable to protect the patented product. An improperly extended patent listed in the Orange Book could also give rise to liability by unjustly deterring a generic drug company from pursuing a competing product³⁶, resulting in higher drug prices for a longer period of time. Other issues include possible license agreement violations, where royalties are normally payable for the life of a licensed patent, including any extensions, or patent misuse if a patent owner seeks to enforce an expired patent or knowingly continues to collect royalties past the expiration date.

Other PTE pitfalls

Another avoidable pitfall arises in calculating the duration of a requested extension. The extension period is based on the regulatory review period—that is, the testing and approval phases preceding FDA approval. The testing phase starts on the effective date of the Investigational New Drug (IND) application (which is required to conduct drug testing in humans) and ends on the filing date of the New Drug Application (NDA). The approval phase begins on the NDA filing date and ends

with the grant of FDA approval. In general, a PTE corresponds to half the number of days in the testing phase plus the total number of days in the approval phase, excluding time periods when the applicant failed to act with “due diligence”³⁷. Although a lack of diligence during drug development can shorten the extension, lawyers should be mindful not to shortchange a PTE applicant unnecessarily.

Yet another tricky point comes in determining the effective start date of the testing period. Drug companies often have several drugs in their pipelines and tend to move resources from one to another, particularly at early stages when it is unclear whether a target candidate will be of sufficient commercial value to proceed. Drug development can also move from one company to another as dictated by business interests, causing the work to proceed in fits and starts. All of these activities and their time periods should be assessed to determine the longest possible extension for which the patent qualifies.

A further PTE nuance relates to the NDA filing date for the drug that is the subject of a PTE application. This date is important because it marks both the end of the testing phase and the start of the approval phase. Forced by the statutory language, the FDA counts this date twice in making a PTE determination—once as the end date of the testing phase, and again as the start date of the approval phase³⁸. For drugs that generate millions of dollars per day, excluding this date in a request for PTE, or suffering from its exclusion if the FDA makes such an error, could be very costly.

PTE practice points

Although it appears that the USPTO and FDA are both becoming more vigilant about the calculation, many PTE applicants and their lawyers are still making mistakes. Unless and until the law is changed, the USPTO, FDA and especially lawyers filing PTE applications should be extremely careful when calculating the 60-day deadline. Clearly, lawyers should file these applications well before the deadline and set their target filing date at least five days before the presumed deadline to avoid the severe consequences of miscalculation. Generic companies on the other hand should always check whether the PTE of a listed patent was properly granted, as the resulting ineligibility could provide them at a minimum with an easy defense (an expired patent cannot be infringed) or even with some ammunition to fight against the brands (e.g., patent misuse).

In assessing due diligence and calculating the duration of a possible PTE, it is particularly important for the PTE application to identify all significant drug development activities and

milestones, regardless of any duration of inactivity that occurs between activity dates. For instance, if activity started but was then stalled for several years, the initial start date should be disclosed to the FDA, as well as any noteworthy activities that may have occurred during the period of relative inactivity. It may also be possible for nontechnical business development practices to be considered evidence of diligent efforts, even if laboratory or clinical testing was not occurring at the time. The applicant is not required to prove due diligence in the first instance, probably because the FDA can rely on its own corresponding records, but providing a complete factual disclosure of all the relevant activities is in the applicant’s best interest as the FDA may calculate a longer regulatory review period, corresponding to a longer PTE, which will be granted if unchallenged for 180 days after publication of the FDA’s calculation (or if the PTE applicant prevails against any such challenge). Notably, the granted length of extension will also be free from later challenge in court, foreclosing a claim of inadequate due diligence as a possible noninfringement defense³⁹. Providing a full description of the relevant facts also complies with the duty of disclosure, which requires the applicant to disclose all information that would be considered “important in determinations to be made in the patent term extension proceeding,” including all “material information adverse to a determination of entitlement to the extension sought”⁴⁰. Such full disclosure can support a good faith request for a longer extension period and might even deter a third party from challenging the extent of PTE granted⁴¹.

For determining the effective start date of the testing period, the PTE applicant should look to the earliest activities related to the product at issue to determine the earliest possible start date. For instance, the testing phase can start when the IND becomes effective (typically 30 days after the IND is filed). If an earlier IND was filed to test a different indication, further investigation should be made to determine if any of the earlier activity (e.g., safety testing) would permit reliance on the earlier start date in calculating the extension period.

For generic drug companies, it is critical to confirm that any grant of PTE was properly made (and was based on a timely filed PTE application) before certifying against an extended patent listed in the Orange Book. If the PTE application was untimely and the original expiration has not yet passed, the generic company might certify that the generic drug will not be marketed before the original expiration date (a “Paragraph III Certification”), which may not require a very long wait. If the original patent term has lapsed, the generic

might be able to certify that the listed patent has expired (a “Paragraph II Certification”), but it is more likely that the FDA would require the generic in this instance to certify that the patent would not be infringed on the grounds that PTE was improperly granted⁴² or is unenforceable because an expired patent cannot be enforced (a “Paragraph IV Certification”). This last type of certification can be extremely valuable because the first abbreviated NDA applicant seeking to gain approval of a generic drug can be rewarded with 180 days of market exclusivity if it includes a Paragraph IV Certification in its application.

COMPETING INTERESTS STATEMENT

The author declares competing financial interests: details accompany the full-text HTML version of the paper at <http://www.nature.com/naturebiotechnology/>.

- Johnson & Johnson Fourth Quarter and Year End 2008 Earnings Meeting (Jan. 20, 2009) <http://files.shareholder.com/downloads/JNJ/531545955x0x264950/c2d48b4a-d107-48ee-b793-0f17ab5033ae/4Q08_WCWeldon_V10_Web.pdf>
- Pfizer Reports Fourth-Quarter And Full-Year 2008 Results And 2009 Financial Guidance (Jan. 26, 2009) <http://media.pfizer.com/files/investors/presentations/q4performance_january012609.pdf>
- AstraZeneca PLC Fourth Quarter and Full Year Results 2008 (Jan. 29, 2009) <http://www.astrazeneca.com/_mshost3690701/content/resources/media/investors/AZN-Q4-2008/q4-results-2008-figures.pdf>
- 35 USC §271.
- 35 USC §156; 21 CFR §60; Drug Price Competition and Patent Term Restoration Act of 1984, tit. II, Pub. L. No. 98–417, 98 Stat. 1585, 1598 (1984) (as amended Dec. 8, 2003).
- 21 USC 355(b).
- Electronic Orange Book (FDA, Washington, DC;). <<http://www.fda.gov/cder/ob>>
- 21 USC §355(j); 21 USC §355(b)(2)
- 35 USC §156(d)(1).
- Online date calculators follow this convention as well. See, e.g. Date Calculator <<http://www.timeanddate.com/date/dateadd.html>>
- USPTO Patent Application Information Retrieval (PAIR) database. <<http://portal.uspto.gov/external/portal/pair>>
- A PTE applicant must identify the filing deadline in its application. 37 CFR §1.740(a)(5).
- Manual of Patent Examining Procedure §2753 (July 2008 revision).
- See Application Pursuant to 35 USC §156(d)(1) and 37 CFR §1.740 For Extension of Patent Term for US Patent No. 5,196,404. <<http://portal.uspto.gov/external/portal/pair>>. This PTE applicant apparently read the statute as reciting a two-month deadline based on its identification of February 15, 2001 as the sixtieth day.
- Letter from USPTO to FDA for US Patent No. 5,196,404 (Mar. 2, 2001) Notice of Final Determination (Nov. 20, 2001). <<http://portal.uspto.gov/external/portal/pair>>
- Decision Denying Application for Patent Term Extension for US Patent No. 5,196,404 at p. 7, n. 3 (Apr. 26, 2007). <<http://portal.uspto.gov/external/portal/pair>>
- 888 F.2d 826 (Fed. Cir. 1989).
- HR 5120, 109th Cong. (2006).
- HR 6344, 110th Cong. §4(a)(1) (as passed by House of Representatives, June 23, 2008).
- Id. at §4(b)(2)(B)
- Cong. Rec. H5811–H5816 (daily ed. Jun. 23, 2008) (statement of Rep. Conyers).
- See Application for Extension of the Term of US Patent No. 4,861,779 Under 35 USC §156 (Nov. 19, 2002). <<http://portal.uspto.gov/external/portal/pair>>
- Letter from FDA to USPTO [re: US Patent No. 4,861,779] (Jul. 16, 2003). <<http://portal.uspto.gov/external/portal/pair>>
- Order to Show Cause [re: US Patent No. 4,861,779] (April 4, 2008). <<http://portal.uspto.gov/external/portal/pair>>
- See Application for Extension of Patent Term Under 35 USC §156 [re: U.S. Patent No. 5,817,338] (Aug. 19, 2003). <<http://portal.uspto.gov/external/portal/pair>>. This PTE application was also rejected on other grounds.
- Letter from FDA to USPTO [re: US Patent No. 5,817,338] (Oct. 19, 2004). <<http://portal.uspto.gov/external/portal/pair>>
- Letter from USPTO to FDA [re: US Patent No. 5,817,338] (Apr. 1, 2008). <<http://portal.uspto.gov/external/portal/pair>>
- Letter from FDA to USPTO [re: US Patent No. 5,817,338] (Oct. 21, 2008). <<http://portal.uspto.gov/external/portal/pair>>
- Petition to the Director (37 CFR §1.181) [re: US Patent No. 5,817,338] (May 30, 2008). <<http://portal.uspto.gov/external/portal/pair>>
- Denial of Patent Term Extension Application [re: US Patent No. 5,817,338] (Dec. 16, 2008). <<http://portal.uspto.gov/external/portal/pair>>
- See Application for Extension of Patent Term Under 35 USC §156 [re: U.S. Patent No. 5,674,860] (Sept. 19, 2003). <<http://portal.uspto.gov/external/portal/pair>>. This PTE application was also rejected on other grounds.
- Letter from FDA to USPTO [re: US Patent No. 5,674,860] (Dec. 6, 2007). <<http://portal.uspto.gov/external/portal/pair>>
- Notice of Final Determination – Ineligible [re: US Patent No. 5,674,860] (Jun. 13, 2008). <<http://portal.uspto.gov/external/portal/pair>>
- Id. at p. 5.
- Request for Reconsideration of Final Determination [re: U.S. Patent No. 5,674,860] (Dec. 16, 2008). <<http://portal.uspto.gov/external/portal/pair>>
- Cf. In re Buspirone Antitrust Litigation, 185 F. Supp. 2d. 340 (improperly listing a patent in the Orange Book associated with potential antitrust liability).
- 35 USC §156(c)(1).
- 37 CFR §1.775(c).
- 35 USC §282.
- 37 CFR §1.765(a).
- MPEP §2753; 35 USC §156(d)(2)(B).
- 35 USC §282.