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FDA, USPTO Data Show Earlier Small-Molecule Drug Patenting

By **Omar Robles and Ji-Won Choi** (December 16, 2020, 5:35 PM EST)

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The Drug Price Competition and Patent Term Restoration Act, known as the Hatch-Waxman Act, had a monumental impact on competition between branded and generic small-molecule pharmaceuticals.[1]

As a general matter, the act provided innovators with certain exclusivities that can prevent the approval and sale of generic versions of a drug product that has been approved under a new drug application, or NDA.[2]

However, patents also play a critical role in so-called brand-brand competition, i.e., competition between typically branded, NDA-approved drugs that are indicated for the same condition and that may have the same mechanism of action.[3]

In both circumstances, a patent holder has an incentive to protect the intellectual property rights to the invention before another can either claim the invention or imitate it.

What's more, since patents have a limited term, there is a dichotomy between patenting inventions both early and late in the drug development process.

The U.S. Food and Drug Administration publication commonly referred to as the Orange Book[4] lists all FDA-approved small-molecule drugs.[5] The Orange Book also identifies, among other things, the periods of statutory exclusivity for which the listed drugs qualify, as well as the patents that the sponsor of the drug's NDA claims protects the drug substance, drug product or product's method of use.[6]

As stated in the antitrust guidelines for the licensing of intellectual property issued by the Federal Trade Commission and the U.S. Department of Justice:

> [I]ntellectual property laws provide incentives for innovation and its dissemination and commercialization by establishing enforceable property rights for the creators of new and useful products, more efficient processes, and original works of expression. In the absence of intellectual property rights, imitators could more rapidly exploit the efforts of innovators and investors without providing compensation. Rapid imitation would reduce the commercial value of innovation and erode incentives to invest, ultimately to the detriment of consumers.[7]

In the context of pharmaceuticals, the ability to patent the innovation that results from risky and costly drug development combined with the ability to commercialize those property rights provides incentives for innovation.

In the absence of those intellectual property rights, imitators could erode incentives to invest in innovation by exploiting the innovators' efforts and, in so doing, discourage the development of new pharmaceuticals. In this specific context, innovators have an incentive to patent an invention early in the development process to preserve the potential commercial opportunity after NDA approval.

However, securing a patent early in the development process may simultaneously reduce the potential commercial opportunity after NDA approval since a patent has a limited term.

Below, we describe salient trends we have found in our analysis of this topic. We have focused on assessing trends in the issuance of patents listed in the Orange Book. Our analysis does not fully unpack the causes and effects of these trends. However, we believe that highlighting the empirical trends we have identified provides important insights.

We have compiled annual electronic snapshots of the Orange Book made available by the FDA from 2011 through 2019, the latter being the final year in which all 12 months of NDA-approval data is available. These snapshots identify the NDA-approved drug products, by product number,[8] that were in the Orange Book during this period, including those the FDA approved before 2011, referred to hereafter simply as drug products.

These snapshots further contain each patent claimed by the drug product sponsors, which we refer to as listing the patent in the Orange Book. We then merged this Orange Book data with supplementary, comprehensive data on the patents granted by the U.S. Patent and Trademark Office.[9]

Trends in Issuance of Listed Patents

Using the merged data set, we investigate whether there is a shift in the timing of patenting for drug products approved between 2011 and 2019. Since drug products can have multiple patents and those patents can be issued across a range of years, our analysis focuses on two distinct questions:

1. When was the first patent issued?

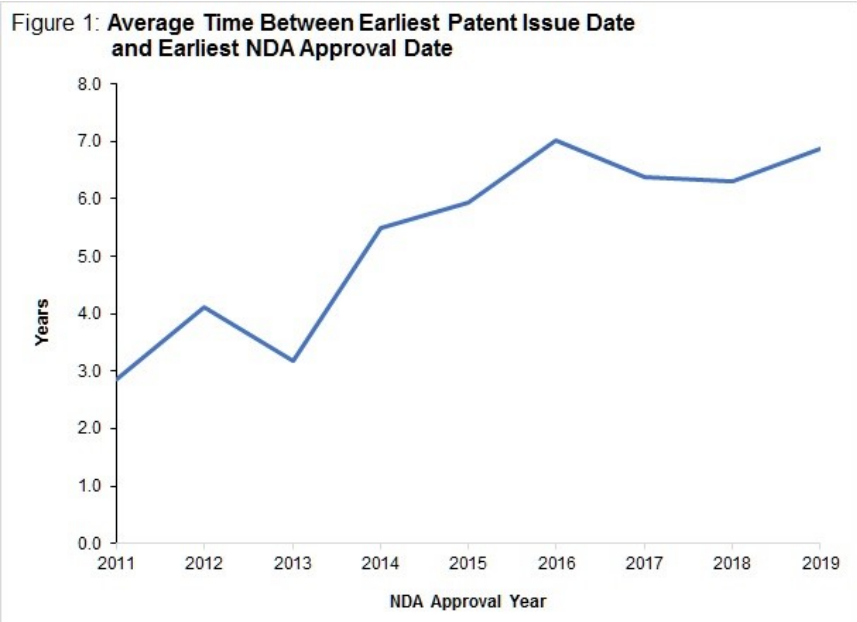
2. When was the last-expiring patent issued?

Exploring these two questions separately allows us to assess overall shifts in the timing of patenting because the issuance dates of the first-issued patent and last-expiring patent will approximate bounds for the salient trends in patenting.[10]

To answer the first question, we examined salient trends in the timing of the first-issued patent that is listed in the Orange Book. Specifically, for each NDA we calculated the number of years between the date of the first patent issuance and the approval date for the NDA or the earliest approval date when multiple drug products were approved on different dates.[11] We will refer to this period as the leading patent period.

For example, if three patents were listed in the Orange Book for an NDA then we would determine which of those three patents was issued first using the USPTO data. To further the example, if the NDA was approved in July 2019 but the first-issued patent for that NDA was issued in July 2017, then we would determine that the leading patent period was 2 years for that NDA.

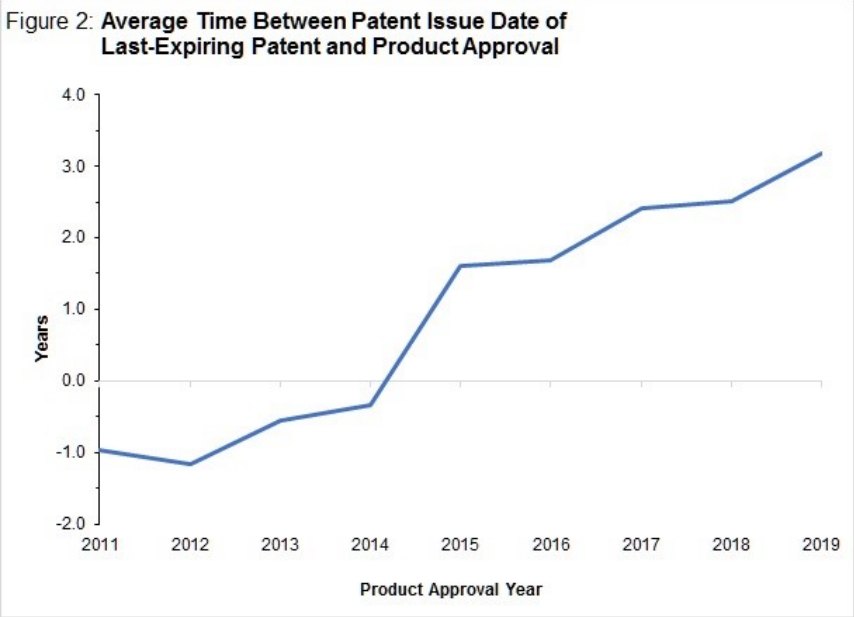
The average leading patent period generally increased from 2011 to 2019. In 2011, the first-issued patent was issued an average of 2.9 years before NDA approval. By 2019, the first-issued patent was issued an average of 6.9 years before NDA approval. These results suggest that, on average, initial patenting has shifted earlier in the drug development process when compared to the timing of NDA approval.[12]



To determine when the last-expiring patent was issued, we examined salient trends in the issue date of the last-expiring patent for a given drug product listed in the Orange Book. Specifically, for each drug product we calculated the number of years between the issue date of the last-expiring patent and the date the drug product was approved by the FDA.[13] We will refer to this period as the latent patent period.

Continuing our earlier example, if three patents were listed in the Orange Book for a drug product, then we determined which of those three patents was the last of the three to expire and then identified the issue date for that patent using the USPTO data. If, for example, the drug product was approved in July 2019 but the last-expiring patent for that drug product was issued in January 2019, then we would determine that the latent patent period was 0.5 years for that drug product.

The average latent patent period also increased from 2011 to 2019. In 2011, the last-expiring patent was issued an average of 1 year after a drug product's approval. This suggests that, on average, the last-expiring patent for a drug product was listed in the Orange Book after NDA approval. By 2019, the last-expiring patent was issued an average of 3.2 years before a drug product's approval. These results suggest that, on average, the issue date of the last-expiring patent has also shifted earlier in the drug development process when compared to the timing of NDA approval.



All told, the results shown in both Figure 1 and Figure 2 suggest that there has been a widespread shift to patenting earlier in the drug development process. This finding raises the question of why this shift has taken place. One possible explanation is that there is a patent race in small-molecule drug development that has resulted in the earlier pursuit of patents. However, there are several additional potential explanations for this trend.

Has the time spent by the FDA to review and approve NDAs increased?

One article published in the Journal of the American Medical Association suggests otherwise. The authors found that FDA drug review times have largely declined since 1983. More recently, the median review time decreased from 1.5 years between 1993 and 2005 to 1.2 years between 2006 and 2017 and fewer than 10.1 months in 2018.[14]

Have clinical trials taken longer to complete, thereby shifting NDA submission forward?

One study based on a comparison of clinical trial cycle times for trials completed between 2006 and 2008, and between 2013 and 2015, found that average Phase II and Phase III cycle times have increased seven months and six months respectively, a combined increase of 1.1 years.

A Nature article on this study states that there are several reasons for these increases, including but not limited to increased complexity and scale of Phase II, as well as outsourcing and expanding to emerging markets in Phase III trials.[15] However, an increase of 1.1 years could not account for the entirety of the salient trend in patenting.

Has the USPTO reduced the time to examine and issue patents?

There are indications of a recent decrease in patent term adjustments, or PTA,[16] which would suggest a decrease in average pendency of patent applications. However, average PTA at peak was estimated to be less than 1.5 years by one account.[17] If the PTA for the Orange Book listed patents has also decreased recently, even a full reduction in PTA could not possibly account for the entirety of the salient trend in patenting.

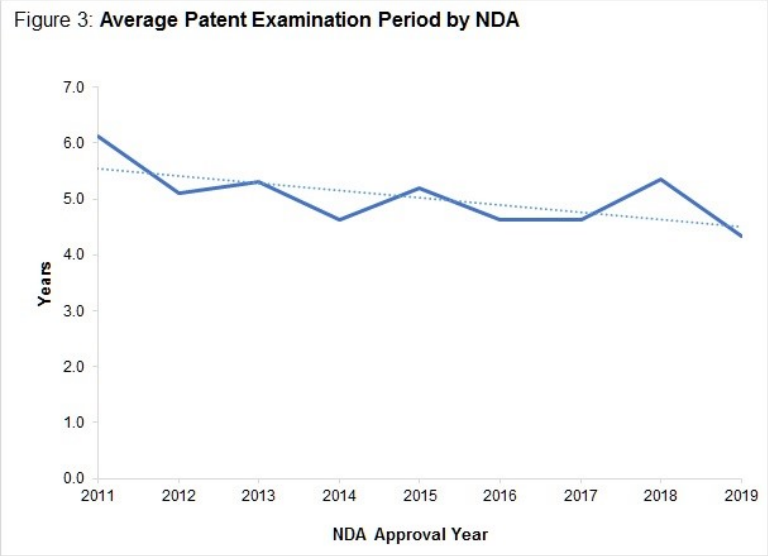
The data we have constructed do allow us to further explore salient trends in average examination time for patents listed in the Orange Book that pertain to recently approved NDAs. Specifically, for each NDA we calculated the number of years between the priority date, i.e., the earliest application filing date associated with a patent, and the issue date of the first-issued patent.[18] We refer to this period as the patent examination period.

Continuing our earlier example, if three patents were listed in the Orange Book for an NDA, then we would determine which of those three patents was issued first using the USPTO data. For that first-issued patent, we would then calculate the amount of time between the priority date and the issue date using, again, the USPTO data. To further the example, if the first patent issued under an NDA was issued in July 2016 and the priority date was July 2010 then we would determine that the patent examination period was 6 years for that NDA.

The average patent examination period generally, but moderately, decreased from 2011 to 2019. In 2011, the patent examination period for the first-issued patent under an NDA was 6.1 years on average. By 2019, the average decreased to 4.3 years. These results suggest that, on average, the examination period for patents pertaining to recently approved NDAs has generally decreased.[19]

However, this decrease could not possibly account for the entirety of the salient trend in patenting we discussed earlier. Between 2011 and 2019, the leading and latent average patent periods increased by approximately 4 to 4.2 years while the average patent examination period decreased by approximately 1.8 years.

Figure 3: **Average Patent Examination Period by NDA**



Concluding Thoughts

We have limited our analysis to the Orange Book snapshots data from the FDA and the patent data from the USPTO. Using this data, we have identified several interesting trends regarding the timing of patent issuance and examination period of patents. In general, we found that, on average, the issue date for patents has shifted earlier in the drug development process when compared to the timing of NDA approval.

We also identified possible causes for this shift: clinical trials may be taking longer; patent examination times may be decreasing; and competition between innovators may have resulted in the earlier pursuit of patents. Our analysis does not fully unpack the causes and effects of these trends. However, we believe that highlighting the empirical trends we have identified provides important insights.

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[1] Drug Price Competition and Patent Term Restoration Act (Public Law 98-417).

[2] See, e.g., "Patents and Exclusivity," FDA/CDER SBIA Chronicles, 19 May 2015, available at https://www.fda.gov/media/92548/download; Rebecca S. Eisenberg, "Patents and Regulatory Exclusivity," The Oxford Handbook of the Economics of the Biopharmaceutical Industry, edited by P. Danzon and S. Nicholson, Oxford: Oxford University Press, 2012, pp. 167–98, available at https://repository.law.umich.edu/book_chapters/126/.

[3] See, e.g., Ameet Sarpatwari, Jonathan DiBello, and Marie Zakarian, et al., "Competition and price among brand-name drugs in the same class: A systematic review of the evidence," PLOS Medicine, available at https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1002872#pmed.1002872.ref006.

[4] The "Orange Book" is officially titled the "Approved Drug Products with Therapeutic Equivalence Evaluations." Although it was first published before the passage of the Hatch-Waxman Act in 1984, the scope of the publication was expanded by its passage. Herein, we refer to the most recent (40th) edition of the Orange Book (available at https://www.fda.gov/media/71474/download) as the "Orange Book 40th Edition."

[5] Orange Book 40th Edition, p. iv.

[6] Orange Book 40th Edition, pp. vi, AD 1; Marianne S. Terrot, "SCP 31 Sharing Session: Publicly Accessible Databases of Patent Status Information concerning Medicines and Vaccines: Overview of the Orange Book and the Off-Patent/Off-Exclusivity List," FDA, available at https://www.wipo.int/edocs/mdocs/scp/en/scp_31/scp_31_h_orange.pdf; "Frequently Asked Questions on Patents and Exclusivity," FDA, available at https://www.fda.gov/drugs/development-approval-process-drugs/frequently-asked-questions-patents-and-exclusivity.

In general, for the included patents, the Orange Book reports the patent number, submission date (i.e., the date the FDA received the request to list the patent), and expiration date. It also reports the expiration date of any statutory exclusivity. Orange Book 40th Edition, pp. AD 2, ADA 1.

[7] "Antitrust Guidelines for the Licensing of Intellectual Property," Federal Trade Commission and the U.S. Department of Justice, available at https://www.justice.gov/atr/IPguidelines/download, p. 2.

[8] A product number is assigned to each drug product associated with an NDA. Drug products available in multiple strengths will have multiple product numbers. "Drugs@FDA Glossary of Terms," FDA, available at https://www.fda.gov/drugs/drug-approvals-and-databases/drugsfda-glossary-terms#P.

[9] The patent data was made available by PatentsView, which "is a patent data visualization and analysis platform intended to increase the value, utility, and transparency of US patent data. The initiative is supported by the Office of Chief Economist in the US Patent & Trademark Office (USPTO)." "About," PatentsView, available at https://www.patentsview.org/web/#.

The data on patents issued by the USPTO was available for patents issued on or after 1976, whereas the patents listed in the Orange Book snapshots were issued on or after 1997. "Patents," PatentsView, http://data.patentsview.org/20200630/download/patent.tsv.zip.

Our analysis is constrained by the static structure of each annual data snapshot of the Orange Book. For each snapshot, NDAs, drug products, and patents that have been discontinued or delisted before the annual snapshot are excluded. Orange Book information is also independent of any current regulatory action being taken administratively or judicially against a drug product.

[10] We use the term "approximate" because patents may sometimes be acquired or licensed by the NDA sponsor after the patents are initially issued to another party.

[11] We began our analysis by identifying the patents listed in the Orange Book for each NDA. We used the comprehensive patent data from the USPTO to determine the issue date for each listed patent and subsequently identified the first-issued patent that was listed in the Orange Book for each NDA.

The structure of our analysis effectively focuses on the first-issued patent for the first-approved drug product(s) under the same NDA. Including all drug products under the same NDA would increase the average patent period to the extent that some drug products are approved years after initial NDA approval while the first-issued patent is listed on all the drug products.

[12] The general result remains the same when our analysis is expanded to include all drug products approved under the same NDA rather than the first-approved drug product for an NDA.

[13] We began our analysis by identifying the patents listed in the Orange Book for each drug product. We used the comprehensive patent data from the USPTO to determine the issue date for each listed patent and subsequently identified the issue date of the last-expiring patent that was listed in the Orange Book for each drug product.

[14] Jonathan J. Darrow, Jerry Avorn, and Aaron S. Kesselheim, "FDA Approval and Regulation of Pharmaceuticals, 1983-2018," JAMA, Vol. 323, No. 2, available at http://sumry.s3.amazonaws.com/uc/2fac1bce9cd34affe633abcd2f33546b_FDAApprovalandRegulationofPharmaceuticals198320181.14.2020.pdf.

[15] Linda Martin, Melissa Hutchens, and Conrad Hawkins, "Clinical trial cycle times continue to increase despite industry efforts," Nature Reviews Drug Discovery, Vol. 16, No. 157, 10 February 2017, available at https://www.nature.com/articles/nrd.2017.21.

[16] Patent Term Adjustment (PTA) is a process of extending the term of a US patent. Its intention is to accommodate for delays caused by the USPTO during the prosecution of a US utility or plant patent application. "Patent Term Adjustment Data August 2020," USPTO, available at https://www.uspto.gov/dashboard/patents/patent-term-adjustment.html#:~:text=Patent%20Term%20Adjustment%20(PTA)%20is,utility%20or%20plant%20patent%20application.

[17] Dennis Crouch, "USPTO Continues to Reduce Patent Term Adjustments," PATENTLYO, available at https://patentlyo.com/patent/2014/08/continues-patent-adjustments.html.

[18] We began our analysis by identifying the patents listed in the Orange Book for each NDA. We used the comprehensive patent data from the USPTO to determine the issue date for each listed patent and subsequently identified the first-issued patent that was listed in the Orange Book for each NDA. We then calculated the time between the priority date and the issue date for the first-issued patents.

The structure of our analysis effectively focuses on the first-issued patent for the first-approved drug product(s) under the same NDA.

[19] The results are generally similar when the analysis is done at the product level as opposed to the NDA level.