JAMA Internal Medicine | Special Communication | HEALTH CARE POLICY AND LAW

Strategies That Delay Market Entry of Generic Drugs

Kerstin Noëlle Vokinger, MD, JD, PhD; Aaron S. Kesselheim, MD, JD, MPH; Jerry Avorn, MD; Ameet Sarpatwari, JD, PhD

Increasing prescription drug expenditures in the United States are primarily driven by high brand-name drug prices. Although generic competition helps lower drug prices, manufacturers of brand-name drugs often work to delay the availability of generic versions of their products. Strategies to forestall generic competition include patenting peripheral aspects of a drug or modified formulations that do not add clinical value, paying generic manufacturers to settle lawsuits challenging the validity of patents on brand-name drugs ("reverse payment" settlements), denying generic manufacturers access to drug samples necessary for bioequivalence testing, misusing risk evaluation and mitigation strategies, and filing citizen petitions with the US Food and Drug Administration (FDA). To address such tactics, the federal government can interpret existing patenting standards more strictly and promote certain types of patent challenges to ensure that patents are granted or upheld only for true innovations. Congress can enact pending legislation that would help discourage reverse payment settlements and compel brand-name manufacturers to share drug samples for bioequivalence testing. Finally, the FDA can provide earlier guidance on bioequivalence determinations for complex generic products and adopt the presumption that late-filed citizen petitions should be summarily rejected.

JAMA Intern Med. doi:10.1001/jamainternmed.2017.4650
Published online September 18, 2017.

Author Affiliations: The Program On Regulation, Therapeutics, and Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

Corresponding Author: Ameet Sarpatwari, JD, PhD, Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, 1620 Tremont St, Ste 3030, Boston, MA 02120 (asarpatwari@bwh.harvard.edu).

In the United States, prescription drugs typically have 2 cycles on the market. The first is the single-source phase, in which only the brand-name manufacturer's version of the drug is available, constituting a government-granted monopoly. The duration of this phase is principally determined by the time remaining on the patents on the drug molecule plus other exclusivity extensions, on average totaling more than 12.5 years for products in wide use.[1] During this period, manufacturers can set any price they wish.[2]

The second, multisource phase starts after the market exclusivity period ends, when the US Food and Drug Administration (FDA) approves bioequivalent and pharmaceutically equivalent versions of the original product made by different manufacturers. These generic drugs are clinically interchangeable with their brand-name counterparts. When multiple generic manufacturers' versions reach the market, the price of the drug can fall by 80% or more, approaching the cost of production.[3]

Market exclusivity periods for brand-name drugs can provide substantial profits, attracting private investment in drug development. After the market exclusivity periods end, however, the availability of generic drugs can lead to reductions in drug prices that are associated with improved medication adherence and health outcomes.[4,5] Utilization of low-cost generic drugs helped save the US health care system an estimated $1 trillion between 1999 and 2010.[6] Yet despite the public health importance of timely availability of generic drugs, manufacturers of brand-name drugs are often able to extend the market exclusivity of their products beyond the period originally anticipated by patent law.

In an earlier article,[7] we considered the determinants of market exclusivity for brand-name drugs. Herein, we examine approaches to delaying market entry of generic drugs, often referred to as "life-cycle management" (or "evergreening"). We reviewed the peer-reviewed medical and health policy literature from January 2006 to January 2017 and references in articles that we determined to be relevant to identify and characterize the strategies that manufacturers of brand-name drugs use to extend market exclusivity. We also discuss practical reforms that could help ensure timely availability of generic drugs.

Background on Generic Drug Approval

The FDA approves generic drugs on the basis of comparisons with the brand-name product that show pharmaceutical equivalence—including the same dosage form and route of administration—and bioequivalence—the absence of clinically relevant differences in the availability of the active ingredient at the site of drug action. Bioequivalence studies usually compare pharmacokinetic measures in healthy volunteers using a single dose of the drug. However, some drugs, such as topical agents, necessitate product-specific approaches to determinations of therapeutic equivalence.[8] Although systematic reviews of FDA-certified generic drugs have found them to be clinically equivalent to the original brand-name products,[9-11] there have been reports of some patients experiencing clinical differences for some narrow therapeutic index drugs, including the anti-epileptic lamotrigine (Lamictal)[12] and the thyroid hormone replacement levothyroxine (Synthroid).[13]

Generic manufacturers usually start bioequivalence testing while the brand-name product is still protected by patents. When submitting their applications to the FDA, generic manufacturers must promise to wait to market their versions until these patents have

expired or allege either that their versions do not infringe these patents or that the patents are invalid. The brand-name manufacturer usually challenges such claims in court.

Every state has drug product selection laws that allow generic drugs to be automatically substituted for brand-name products at the pharmacy. These laws authorize—and in some cases require—pharmacists to dispense available bioequivalent generics when prescriptions are written for brand-name drugs and do not include an explicit instruction from physicians to "dispense as written."[14] Because generic products are often made by many manufacturers and generally have low profit margins, they are usually not advertised; instead, such products compete on price.

Strategies to Extend Market Exclusivity

Secondary Patenting

Since the length of a brand-name drug's market exclusivity is primarily based on the patents covering the product, a common approach to delay the availability of generic drugs is to obtain new patents on peripheral aspects of the drug or its use. These secondary patents may cover such features as a drug's coating, salt moiety, formulation, or method of administration. Under federal law, the US Patent and Trademark Office (USPTO) may grant patents only to products that are novel and nonobvious. From 1985 to 2005, the median number of patents listed with the FDA per new molecular entity increased from 1 to 3.[15] Sometimes, these patents cover products that offer meaningful therapeutic advances, but many do not even though they may meet the statutory requirements for earning a patent.[16] For example, in an attempt to extend market exclusivity for the transformative chronic myelogenous leukemia treatment imatinib (Gleevec), Novartis replaced its original product with a new version featuring a different crystal of the active ingredient covered by secondary patents, but the modified version did not offer improvements in effectiveness or safety over the original version.[17]

Modifications that lead to distinct drug products offer the greatest possibility for clinical benefits. A drug originally developed to take 2 or 3 times a day that is modified to a once-a-day formulation, for example, can help improve patient adherence. But the introduction of such products has also sparked controversy when the brand-name manufacturer has simultaneously undermined the market for the older formulation. One such case involved Forest Laboratories, which sold memantine (Namenda), an immediate-release, twice-daily treatment for Alzheimer disease. Before a generic was released, Forest received separate FDA approval for a patented, once-daily version of the drug—memantine XR—while also announcing its intention to remove the original product from the market. This action would have forced physicians to switch patients from memantine to memantine XR, undercutting subsequent automatic substitution of a generic for brand-name memantine. The New York Attorney General sued to prevent this "product hop," and a federal court of appeals required Forest to continue selling the immediate-release version of memantine at least until a generic became available.[18]

Reverse Payment Settlements

Another way for brand-name drug manufacturers to extend their market exclusivity is by settling litigation related to the validity of their patents. The most controversial kind of settlement involves agreements in which generic manufacturers agree to drop their legal challenges to brand-name manufacturers' patents and then market their products later than might have been anticipated if their litigation was successful in return for compensation. These deals are called "reverse payment" settlements (or "pay-for-delay" settlements), since payments in patent litigation cases usually move from the patent challenger to the patent holder. Between 2001 and 2008, the number of patent challenges by generic manufacturers increased 471%, from 35 to 165,[19] which was matched by a similar increase in such settlements.[20] Although reverse payment settlements can avoid lengthy litigation, the Federal Trade Commission (FTC) estimated in 2010 that they would cost American consumers $3.5 billion annually in forgone savings over the next decade by preventing or delaying the availability of more affordable generic products.[20] In the 2013 case *FTC v Actavis*, the Supreme Court ruled that reverse payment settlements were subject to antitrust review.[21] Although reverse payment settlements have become less common after this ruling (40 in 2012; 29 in 2013; 21 in 2014),[22] they have not ended but have continued as more complex comarketing agreements that are "meant to obscure the fact the generic firm is still receiving large consideration in return for delay."[23(p516)]

The new forms of reverse payment settlements can involve agreements related to "authorized generics," brand-name drugs that are marketed or distributed as generic medications, either by a subsidiary of the brand-name manufacturer or by a generic manufacturer licensed by it. Authorized generic drugs generally become available around the time that generics are due to enter the market. They can reduce the revenue of the first generic entrant by as much as 60% during the first 6 months after the loss of market exclusivity.[24] One recent example of a "no authorized generic" reverse payment settlement involved Warner Chilcott, which offered to forgo making an authorized generic of its contraceptive ethinyl estradiol–norethindrone (Loestrin 24 Fe) in exchange for Watson delaying sale of its generic version of the drug.[25]

Restrictions on Drug Distribution

A manufacturer of a brand-name drug can also extend its market exclusivity by restricting generic manufacturers' access to its drug for required bioequivalence testing, blocking a generic manufacturer's ability to complete its application to the FDA. For example, under restricted drug distribution networks, patients can receive a drug only through a single specialty pharmacy or multiple certified pharmacies. The stated reasons for such networks may be to increase efficiency in distribution for niche products or to allow the manufacturer to comply with risk evaluation and mitigation strategies (REMS), programs that the FDA has had the power to apply to drugs with known or suspected safety risks since 2007. However, a brand-name manufacturer can also use a restricted distribution network to prevent potential generic competitors from acquiring sufficient drugs samples to conduct bioequivalence testing, a prerequisite for generic drug approval. Although the FTC considers refusing to supply competitors with drug samples as an illegal restraint of trade, the FDA had received approximately 150 inquiries from generic manufacturers about their inability to secure sufficient samples as of March 2016.[26]

REMS can be misused in other ways to block generic entry. Manufacturers of brand-name and generic drugs are encouraged to operate a single, shared REMS for drugs posing severe risks, such as extended-release and long-acting opioids. Several manufacturers of brand-name

drugs, however, have refused to engage in or intentionally drawn out discussions over the framework for such shared systems, thereby delaying FDA approval of generic drug applications.[26] For example, in responding to a request by Reckitt to deny approval of nonfilm formulations of the partial opioid agonist buprenorphine-naloxone (Suboxone), the FDA noted generic manufacturers' allegations that the company "feigned cooperation with the shared REMS development process and used deceptive tactics for months to hide its true intent, which was to delay the generic industry from obtaining" approvals.[27]

Other manufacturers have patented their REMS.[28] Celgene, for example, obtained multiple patents on its REMS for thalidomide (Thalomid), which aims to prevent exposure of the well-known teratogen among pregnant women through education, mandatory pregnancy testing, and dispensing restrictions. When Barr Laboratories sought to market a generic version of the drug, Celgene filed suit, claiming that these patents would be infringed.[28]

Citizen Petitions

Manufacturers of brand-name drugs have also creatively used so-called citizen petitions to delay the marketing of generic drugs.[29] These petitions allow individuals or groups—including companies—to request the FDA to take or refrain from taking an administration action. Between 2011 and 2015, the FDA received 124 citizen petitions pertaining to pending generic applications; of these, manufacturers of brand-name drugs filed 108 (87%).[30] Many of the petitions related to drugs that are complex to copy—including dermatologic formulations or medications that act locally in the gastrointestinal tract (instead of being absorbed systemically). A typical argument was that the FDA's normal bioequivalence testing process was insufficient, and that the agency should therefore refrain from approving the application without further testing.[31] In one case, a brand-name manufacturer filed 24 different citizen petitions to the FDA between 2006 and 2012 to delay FDA approval of a generic version of oral vancomycin (Vancocin), commonly used to treat *Clostridium difficile*–associated diarrhea.[32]

In response to petitions it receives, the FDA usually conducts in-depth investigations that may delay generic approvals. In a 2016 report to Congress, for example, the FDA stated that citizen petitions resulted in 5 delayed drug approvals between 2013 and 2015.[33] Although such petitions can raise issues about bioequivalence and the potential need for additional testing, only 3 of 67 (4%) decided over this period were approved.[30]

Policy Solutions

To promote efficient transitions to generic competition after a drug's market exclusivity ends, reforms could target the review of patents; reverse payment settlements; and the misuse of restricted distribution programs, REMS, and citizen petitions.

Patent Oversight

If the USPTO were to apply a stricter interpretation of the existing novelty and nonobviousness standards, weak secondary patents covering trivial drug modifications would be less likely to be granted.[34,35] Recent Supreme Court decisions reining in lax interpretations of basic patenting standards for diagnostic tests and DNA sequencing suggest that such a change might be possible.[36-38] In the 2012 case, Mayo v Prometheus, for example, the Court rejected patent claims on methods for determining the optimal dose of thiopurine drugs to treat autoimmune diseases, holding that the steps involved "add nothing of significance to the natural laws themselves."[36(p1302)]

The federal government could also support challenges to questionable secondary patents under "inter partes review,"[39] a pathway created by the 2012 America Invents Act. Inter partes review offers several advantages over traditional litigation. For example, anyone can bring a challenge. The Patent Trial and Appeal Board, an administrative body of experts intended to be more familiar with complex scientific and patenting issues than judges in federal district court, conducts reviews. In addition, resolution of the reviews is usually faster than through the federal courts—a maximum, of 18 months—and thus less expensive.

Initial data reveal the promise of inter partes review in reducing meritless patents. Between September 2012 and March 2016, 18% of petitions for review (790 of 4288) had a final written decision; 73% of the decisions invalidated the patent.[40] The long-term viability of this strategy will depend on a pending Supreme Court case on whether it is constitutional for a nonjudicial body like the Patent Trial and Appeal Board to terminate patent rights.

Finally, the federal government can invoke its rights to use patented products, although in recent years it has not done so. Under an authority often compared with eminent domain power over land, the federal government may seek out alternative manufacturers of patented products for use in programs like Medicare and Medicaid, provided it offers reasonable compensation to the patent holder.[41] This intervention has primarily been suggested in the context of high-priced, brand-name drugs addressing pressing public health issues, such as the hepatitis C drug sofosbuvir (Sovaldi).[42] However, it could also be applied to facilitate product entry when a manufacturer of brand-name drugs is using REMS patents to block competition.

When the federal government or one of its grantees is listed as an inventor on the patent, the federal government can also consider exercising "march-in" rights, relating to an exclusive license of the patent under the Bayh-Dole Act of 1980.[43] March-in rights allow the government to ignore the exclusive license and grant additional licenses to other reasonable applicants. The federal government, however, has never exercised such rights and indeed has invoked the prospect of generic competition on the horizon as a reason for rejecting march-in rights petitions.[44]

Curbing Reverse Payment Settlements and REMS Misuse

Legal rulings in the wake of the 2013 *Actavis* case, which made reverse payment settlements subject to antitrust review, make clear that antitrust scrutiny applies to non-cash reverse payment settlements.[25,45] In 2016, the FTC filed its first complaint regarding a settlement that included a "no authorized generic" provision against several manufacturers. One, Endo Pharmaceuticals, allegedly used the settlement to block generic versions of its 2 top-selling drugs, Lidoderm, a lidocaine topical patch to relieve pain from postherpetic neuralgia, and Opana ER, an extended-release formulation of oxymorphone.[46] To resolve the FTC's investigation, Endo and another manufacturer agreed to abandon these settlements.[47]

Congress can assist in this effort. In 2017, Senators Amy Klobuchar and Charles Grassley reintroduced the Preserve Access to Affordable Generics Act,[48] which would create a presumption that reverse pay-

ment settlements are anticompetitive and require parties to such settlements to disclose all other agreements they have entered into within the same timeframe as the settlement. Parties that settle Patent Trial and Appeals Board challenges should also have to file similar agreements with the FTC for review.

Separate proposed legislation would help combat the misuse of REMS. In 2017, Senator Patrick Leahy (and 11 cosponsors) introduced the Creating and Restoring Equal Access to Equivalent Samples (CREATES) Act, which would require manufacturers to share samples of their products on "commercially reasonable terms" with other manufacturers seeking to perform bioequivalence testing.[49] Brand-name manufacturers should also be required to provide a royalty-free license for use of their REMS to generic manufacturers as needed. Although prior versions of the Preserve Access to Affordable Generics Act and the CREATES Act have failed to advance, the increasing burden of high-cost prescription drugs on consumers may provide Congress with the necessary impetus to enact these measures in 2017.

Rethinking the Citizen Petition Process

To address the misuse of citizen petitions, the FDA can provide guidance about the types of tests needed to determine bioequivalence for complex generic products well in advance of when the primary patent expires. Funding for such work could be included in the pending renewal of the Generic Drug User Fee Act.

Under federal law, the FDA can already summarily deny a citizen petition filed "with the primary purpose of delaying the approval of an application" and which "does not on its face raise valid scientific or regulatory issues."[50] Given its experience, the agency could adopt the presumption that late-filled petitions filed by brand-name manufacturers should be rejected, and, before proceeding to a full review, require a preliminary finding that the petitions will likely be granted

Conclusions

Manufacturers of brand-name drugs use many strategies to extend the market exclusivity of their products, extending the terms of government-granted monopolies beyond those originally intended by patent law. By delaying the entry of generic products into the marketplace, such tactics can keep prices high and limit the affordability of drugs to patients and payers. In addition, such policy lapses unintentionally create economic incentives for manipulating the patent terms on older products, rather than incentives for the discovery of new treatments. Policy reforms to address these strategies include stricter interpretation of patenting standards, challenges to secondary patents, restrictions on reverse payment settlements and the misuse of restricted distribution programs and REMS, earlier guidance on bioequivalence determinations for complex generic products, and summary rejection of last-minute citizen petitions. Implementation of any combination of these reforms should help to improve the timely availability of generic drugs and encourage investment in the next generation of therapeutic products.

ARTICLE INFORMATION

Accepted for Publication: July 31 2017.

Published Online: September 18, 2017. doi:10.1001/jamainternmed.2017.4650

Conflict of Interest Disclosures: None reported.

Funding/Support: This work was supported by the Commonwealth Fund. Dr Kesselheim's and Dr Sarpatwari's work is also funded by the Laura and John Arnold Foundation and the Engelberg Foundation. Dr Vokinger has received grants from the Swiss National Foundation for Scientific Research. Dr Kesselheim has received grants from the FDA Office of Generic Drugs and Division of Health Communication.

Role of the Funder/Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

REFERENCES

1. Grabowski H, Long G, Mortimer R. Recent trends in brand-name and generic drug competition. *J Med Econ*. 2014;17(3):207-214.

2. Kesselheim AS, Avorn J, Sarpatwari A. The high cost of prescription drugs in the United States: origins and prospects for reform. *JAMA*. 2016;316(8):858-871.

3. US Food and Drug Administration. Generic competition and drug prices. https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm129385.htm. May 13, 2015. Accessed July 24, 2017.

4. Shrank WH, Hoang T, Ettner SL, et al. The implications of choice: prescribing generic or preferred pharmaceuticals improves medication adherence for chronic conditions. *Arch Intern Med*. 2006;166(3):332-337.

5. Gagne JJ, Choudhry NK, Kesselheim AS, et al. Comparative effectiveness of generic and brand-name statins on patient outcomes: a cohort study. *Ann Intern Med*. 2014;161(6):400-407.

6. Drug pricing: research on savings from generic drugs use. Government Accountability Office. http://www.gao.gov/assets/590/588064.pdf. January 31, 2012. Accessed July 24, 2017.

7. Kesselheim AS, Sinha MS, Avorn J. Determinants of market exclusivity for prescription drugs in the United States [published online September 11, 2017]. *JAMA Intern Med*. doi:10.1001/jamainternmed.2017.4329

8. Lionberger RA. FDA critical path initiatives: opportunities for generic drug development. *AAPS J*. 2008;10(1):103-109.

9. Manzoli L, Flacco ME, Boccia S, et al. Generic versus brand-name drugs used in cardiovascular diseases. *Eur J Epidemiol*. 2016;31(4):351-368.

10. Kesselheim AS, Misono AS, Lee JL, et al. Clinical equivalence of generic and brand-name drugs used in cardiovascular disease: a systematic review and meta-analysis. *JAMA*. 2008;300(21):2514-2526.

11. Kesselheim AS, Stedman MR, Bubrick EJ, et al. Seizure outcomes following the use of generic versus brand-name antiepileptic drugs: a systematic review and meta-analysis. *Drugs*. 2010;70(5):605-621.

12. Privitera MD, Welty TE, Gidal BE, et al. Generic-to-generic lamotrigine switches in people with epilepsy: the randomised controlled EQUIGEN trial. *Lancet Neurol*. 2016;15(4):365-372.

13. Dong BJ, Hauck WW, Gambertoglio JG, et al. Bioequivalence of generic and brand-name levothyroxine products in the treatment of hypothyroidism. *JAMA*. 1997;277(15):1205-1213.

14. Sarpatwari A, Kesselheim AS. The case for reforming drug naming: should brand name trademark protections expire upon generic entry? *PLoS Med*. 2016;13(2):e1001955.

15. Hemphill CS, Sampat BN. Weak patents are a weak deterrent: patent portfolios, the Orange Book listing standard, and generic entry. National Bureau of Economic Research. http://www.nber.org/chapters/c13215.pdf. December 2011. Accessed August 18, 2017.

16. Amin T, Kesselheim AS. Secondary patenting of branded pharmaceuticals: a case study of how patents on two HIV drugs could be extended for decades. *Health Aff*. 2012;31:2286-2294.

17. *Novartis AG v Union of India*, 6 SCC 1-112 (2013).

18. *New York v Actavis*, 787 F.3d 638 (2d Cir 2015).

19. Higgins MJ, Graham SJH. Intellectual property. Balancing innovation and access: patent challenges tip the scales. *Science*. 2009;326(5951):370-371.

20. Federal Trade Commission. Pay-for-delay: how drug company pay-offs cost consumers billions. https://www.ftc.gov/sites/default/files/documents/reports/pay-delay-how-drug-company-pay-offs-cost-consumers-billions-federal-trade-commission-staff-study/100112payfordelayrpt.pdf. January 2010. Accessed July 24, 2017.

21. *Federal Trade Commission v Actavis*, 133 S Ct 2223 (2013).

22. Federal Trade Commission. Agreements filed with the Federal Trade Commission under the Medicare Prescription Drug, Improvement, and Modernization Act of 2003: overview of agreements filed in fiscal year 2014. https://www.ftc.gov/system/files/documents/reports/agreements-filled-federal-trade-commission-under-medicare-prescription-drug-improvement/160113mmafy14rpt.pdf. January 2016. Accessed July 24, 2017.

23. Feldman R, Frondorf E. Drug wars: a new generation of generic pharmaceutical delay. *Harvard J Legis*. 2016;53:499-561.

24. Federal Trade Commission. Authorized generic drugs: short-term effects and long-term impact. https://www.ftc.gov/sites/default/files/documents/reports/authorized-generic-drugs-short-term-effects-and-long-term-impact-report-federal-trade-commission/authorized-generic-drugs-short-term-effects-and-long-term-impact-report-federal-trade-commission.pdf. August 2011. Accessed July 24, 2017.

25. In re Loestrin 24 FE Antitrust Litigation, 814 F3d 538 (1st Cir 2016).

26. Dabrowska A. FDA risk evaluation and mitigation strategies (REMS): description and effect on generic drug development. Congressional Research Service. https://www.everycrsreport.com/reports/R44810.html. April 11, 2017. Accessed July 24, 2017.

27. FDA/CDER to Reckitt Benckiser Pharmaceuticals Inc—denial. Regulations.gov. https://www.regulations.gov/document?D=FDA-2012-P-1028-0011. February 22, 2013. Accessed July 24, 2017.

28. Sarpatwari A, Avorn J, Kesselheim AS. Using a drug-safety tool to prevent competition. *N Engl J Med*. 2014;370(16):1476-1478.

29. Feldman R, Wang C. A citizen's pathway gone astray: delaying competition from generic drugs. *N Engl J Med*. 2017;376(16):1499-1501.

30. Carrier M, Minniti C. Citizen petitions: long, late-filed, and at-last denied. *Am Univ Law Rev*. 2017;66(2):305-352.

31. Kesselheim AS, Gagne JJ. Product-specific regulatory pathways to approve generic drugs: the need for follow-up studies to ensure safety and effectiveness. *Drug Saf*. 2015;38(10):849-853.

32. Federal Trade Commission. FTC charges that Shire ViroPharma Inc abused government processes through serial, sham petitioning to delay generics and maintain its monopoly over Vancocin HCl capsules. https://www.ftc.gov/news-events/press-releases/2017/02/ftc-charges-shire-viropharma-inc-abused-government-processes. February 7, 2017. Accessed July 24, 2017.

33. US Food and Drug Administration. Report to Congress: Eighth annual report on delays in approvals of applications related to citizen petitions and petitions for say of agency action for fiscal year 2015. https://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ReportsBudgets/UCM517279.pdf. July 29, 2016. Accessed July 24, 2017.

34. Furrow ME. Pharmaceutical patent life-cycle management after KSR v. Teleflex. *Food Drug Law J*. 2008;63(1):275-320.

35. Correa CM. Guidelines for pharmaceutical patent examination: examining pharmaceutical patents from a public health perspective. http://www.undp.org/content/dam/undp/library/HIV-AIDS/UNDP_patents_final_web_2.pdf?download. 2016. Accessed August 18, 2017.

36. *Mayo v Prometheus*, 132 S Ct 1289 (2012).

37. *Association for Molecular Pathology v Myriad Genetics*, 133 S Ct 2107 (2013).

38. Cook-Deegan R, Chandrasekharan S, Angrist M. The dangers of diagnostic monopolies. *Nature*. 2009;458(7237):405-406.

39. Treasure CL, Kesselheim AS. How patent troll legislation can increase timely access to generic drugs. *JAMA Intern Med*. 2016;176(6):729-730.

40. Grewal M, Hill J, Zalewski J. Trends in inter partes review of life sciences patents. *BNA Patent Trademark Copyright J*. 2016;92(2266):1-4.

41. Brennan H, Kapczynski A, Monahan C, Rizvi Z. A prescription for excessive drug pricing: levering government patent use for health. *Yale J Law Tech*. 2016;18(1):275-354.

42. Tribble SJ. Louisiana proposes tapping a federal law to slash hepatitis C drug prices. Kaiser Health News. http://khn.org/news/louisiana-proposes-tapping-a-federal-law-to-slash-hepatitis-c-drug-prices/. May 4, 2017. Accessed June 29, 2017.

43. 35 USC § 302 (2012): March-in rights.

44. Treasure CL, Avorn J, Kesselheim AS. Do march-in rights ensure access to medical products arising from federally funded research? a qualitative study. *Milbank Q*. 2015;93(4):761-787.

45. *King Drug Co. Florence v SmithKline Beecham*, 791 F3d 388 (3rd Cir 2015).

46. Federal Trade Commission. Endo Pharmaceuticals Inc. agrees to abandon anticompetitive pay-for-delay agreements to settle FTC charges; FTC refiles suits against generic defendants. https://www.ftc.gov/news-events/press-releases/2017/01/endo-pharmaceuticals-inc-agrees-abandon-anticompetitive-pay-delay. January 23, 2017. Accessed July 20, 2017.

47. Federal Trade Commission v Teikoku Pharma USA, Case 2:16-cv-01440-PD (March 30, 2016). https://www.ftc.gov/system/files/documents/cases/160331endoorder.pdf. Accessed July 31, 2017.

48. S 124, 115th Cong (2017).

49. S 974, 115th Cong (2017).

50. 5 USC § 355(q)(1)(E) (2012): Denial based on intent to delay.