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Drugs

The biological systems we most care about – living human bodies – are complicated beyond our present understanding and also so precious that experiments on them cannot be undertaken lightly. This means that biological innovation is often slow and amazingly expensive, but also amazingly valuable when successful. These facts inflect the IP system in some important ways. Most importantly, they give rise to an extensive and intensive regulatory regime that restricts how drugs and similar medical technologies are researched and commercialized. Like a supertanker steaming through a boat pond, this regime has drawn the intellectual property system along into its wake.

A Approval

The Food and Drug Administration oversees one of the most intensive regulatory regimes in the whole of the U.S. Code.¹ A “new drug,” for example, cannot be shipped in interstate commerce unless it has gone through the FDA approval process. Why does this matter to an IP course?² First, because the structure of regulatory approval changes the IP strategies of actors affected by it. Second, because Congress has rewritten the patent laws to take account of the realities of regulatory approval for certain products. (*Eli Lilly & Co. v. Medtronic, Inc.* summarizes.) Third, because the regulatory approval gateway is itself a source of IP-like rights, which can give one company the effectively exclusive right to use the information embedded in its drug product. And fourth, because Congress has created entirely new forms of informational exclusivity to deal with the wrinkles of the system.

1 Drug Patents

The modern drug regulatory regime is, in one sense, oriented towards patent as its preferred form of intellectual property. But its demands have also compelled patent law to adapt to better fit.

1. Cf. Anna B. Laakmann, *A Property Theory of Medical Innovation*, 56 *Jurimetrics J.* 117 (2016); Robin Feldman, *Regulatory Property: The New IP*, *Colum. J.L. & Arts* (forthcoming)
2. There are similar but different regulatory regimes for the approval of animal drugs; of medical devices like syringes, pacemakers, and diagnostic tests; and of “biological products” like vaccines, blood plasma, and genetic therapies. We focus on drugs in this section because they illustrate all of the essential issues. There’s a quick hit on biologics a little further down.

Within the nineteenth-century food and drug markets, the predominant use of intellectual property was to protect medicines. Patents were not, however, the preferred means of protecting commercial interests in medicines. Despite the use of the term "patent medicines" to describe nineteenth-century nostrums, only a small percentage of medicines were patent-protected in the nineteenth century. What were widely referred to as "patent medicines" during the nineteenth and early twentieth centuries were usually not patented. "Patent medicines" referred to proprietary medicines, medicines sold by only one manufacturer, containing a secret combination of ingredients. A historian of the entrepreneurs who sold such nostrums in the nineteenth and twentieth centuries has argued that only the least savvy sought patent protection for their recipes.

No one but the manufacturer knew what was in the pills, liquids, or ointments sold. When patients bought such medicines as self-treatment, or, as often happened, when physicians prescribed them, neither prescribing doctor nor patient knew what was being ingested. Instead, both relied upon advertising copy about the powers of the medicine and the recommended dosage.

Secrecy allowed the manufacturer to hide, for example, the fact that the medicine contained mostly water, or common household ingredients, or significant amounts of alcohol, the revelation of which, it was argued, would drive away consumers. Doctors and pharmacists further alleged that manufacturers had no compunction about changing the ingredients of a medicine to respond to fluctuations in prices of ingredients, while continuing to sell it under the same packaging, using the secrecy of their formulas to disguise shifting compositions. Businessmen bought and sold trade names rather than secret formulas, patents, or manufacturing know-how as they sought to maximize profits.

Elite regular physicians contrasted proprietary medicines based on secrecy against what they called "ethical" medicines. These medicines were the formulary medicines, known parts of the *materia medica*. These medicines were listed in the *United States Pharmacopeia* or the *National Formulary*, and, if mixtures, could be compounded by any druggist based on published formulae. They, too, were sold under brand names that could be protected as trademarks, but the brand name identified the manufacturer, not the particular product. These so-called ethical manufacturers who built businesses on supplying doctors and pharmacists with consistent, good quality supplies of formulary drugs were a small part of the drug market." By the turn of the twentieth century, as the campaign of regular physicians against proprietary medicines gained strength, the ethical medicines were also defined by their advertisement to physicians, rather than directly to the public.

Regular physicians had long criticized the sale and use of proprietary medicines, even as medical journals accepted advertisements from their manufacturers and many doctors wrote prescriptions for such medicines. The critiques generally fell into three categories: (1) such nostrums were sold for far more than the value of their ingredients,

and therefore were a fraud on the public's pocketbook; (2) such nostrums actively harmed their users by containing powerful drugs such as morphine; and (3) such nostrums in no way fulfilled the promises made on their labels and in their elaborate advertisements, like claims to cure cancer, tuberculosis, and syphilis. At best, consumers were being hoodwinked, and at worst, they were poisoning themselves and their children.

A campaign for comprehensive federal regulation began in earnest in 1879, when the first federal food and drug bill was introduced into Congress. From that year until 1906, such a bill was unsuccessfully introduced into every Congress. The 1906 Act as finally passed outlawed the interstate shipment of "adulterated" or "misbranded" food or drugs and their manufacture within the District of Columbia and the territories.

The proprietary medicine manufacturers quickly reduced the Act's regulatory power to inhibit their business model by winning the case.³ In his opinion, Justice Oliver Wendell Holmes declared that Congress had not intended to consider any claims about therapeutic value made on product labels as false or misleading, for such were merely matters of opinion, not susceptible to examination by the Bureau of Chemistry. Thus, manufacturers could continue to fill their labels with broad claims of cure. Congress attempted to strengthen the regulation of false claims of therapeutic value by passing the Sherley Amendment in 1912. This fix, however, failed to fully correct the problem, as the courts interpreted the language of the amendment prohibiting "false and fraudulent" claims to require a showing of intentional falsehood. While the FDA did pursue egregious claims of cure, with so many testimonials as to the value of their products, manufacturers could easily avoid a jury finding of intentional falsehood.

After two decades of agitation and five years of effort within the FDR administration, the new bill, the Federal Food, Drug, and Cosmetic Act, passed in 1938. The new Act was much longer and more detailed, as its drafters had sought to close perceived loopholes in the first regulatory scheme. All drugs had to bear a label with "an accurate statement of the quantity of the contents in terms of weight, measure, or numerical count" as well as the name and address of the manufacturer or distributor. Most significantly, for any non-formulary drug, the "common or usual name" of each active ingredient had to be listed on the label. Finally, many ingredients of proprietary medicines would be revealed to the public, even if the exact formulae were not.

From a contemporary perspective, we might assume that the purity campaign, as a campaign against trade secrets, would embrace patents as a better intellectual property regime. Patents are often understood as a complementary choice to trade secrets, offering a strong limited-term monopoly in exchange for public disclosure. Today, we are very familiar with the arguments for the use of patents to protect pharmaceuticals—patents allow a period of exclusive sales during which time the originator of a new medicine reaps monopoly pricing as a just reward for a

3. *United States v. Johnson*, 221 U.S. 488 (1911).

large investment in research and development, providing the necessary reward to incentivize the risky and expensive process of drug development. Once the drug comes off patent, other manufacturers can make and sell the same drug, causing the price paid by consumers to drop.

In 1938, as the world of laboratory-created drugs was just emerging, this argument was not yet dominant. Instead, Americans, and particularly American doctors and pharmacists, were familiar with another argument regarding patents and medicines, an argument that had persisted over the previous century. This older argument described “medical patents” – a term which lumped together any patents to medicines, methods of treatment, and medical devices – as unethical.

Yet, the new scientific ways of knowing had changed the landscape of both trade secrets and patents within the drug market. Chemistry made keeping secrets from competitors much more difficult. The proprietary medicines could be analyzed and their contents publicized. Manufacturers did not even necessarily need to do this work themselves; the AMA did some of this analysis and publication as part of its campaign against secrecy.

The remarkable aspect of the late 1930s in retrospect is not that medical patents became commonplace, unopposed by both the ethical manufacturers and organized medicine, but that for a brief window of time, the medical profession envisioned medical patents allowing a medically controlled drug marketplace. Rather than seeing patents as an unmitigated evil, allowing the privatization of what should be used for the public benefit, the medical profession saw them as a way of increasing its own authority, a counterweight to the profit-oriented firms and the useful, but medically uninformed, federal bureaucrats in the FDA and the patent office. Instead of patents making medical professionals unethical, the control of patents by ethical professionals would make patents, now perceived as necessary aspects of a new, more complicated pharmacopeia, ethical.

Instead, through the federal food and drug regulation and the new science, doctors traded a drug marketplace dominated by secret proprietaries that offered little therapeutic value for a drug marketplace dominated by new corporatized proprietaries that offered medical miracles. Organized medicine had to be content with the control it would increasingly gain as prescription drugs became a legal category. As self-dosing became less common, doctors became the key gatekeepers on the demand side of the burgeoning market in pharmaceuticals. During the course of the twentieth century, doctors gained the ability to control their patient’s access to medications, but lost any hope that doctors or medically controlled organizations would exercise control over the supply side. What medications were available for doctors to prescribe would be determined by the drug companies and the FDA.

Merck KGaA v. Integra Lifesciences I, Ltd.

545 U.S. 193 (2005)

The Federal Food, Drug, and Cosmetic Act (FDCA)⁴ regulates the manufacture, use, or sale of drugs. Under the FDCA, a drugmaker must submit research data to the FDA at two general stages of new-drug development. First, a drugmaker must gain authorization to conduct clinical trials (tests on humans) by submitting an investigational new drug application (IND). The IND must describe “preclinical tests (including tests on animals) of the drug adequate to justify the proposed clinical testing.”⁵ Second, to obtain authorization to market a new drug, a drugmaker must submit a new drug application (NDA), containing “full reports of investigations which have been made to show whether or not the drug is safe for use and whether the drug is effective in use.”⁶ Pursuant to FDA regulations, the NDA must include all clinical studies, as well as preclinical studies related to a drug’s efficacy, toxicity, and pharmacological properties.

Eli Lilly & Co. v. Medtronic, Inc.
496 U.S. 661 (1990)

Under federal law, a patent “grant[s] to the patentee, his heirs or assigns, for the term of seventeen⁷ years, . . . the right to exclude others from making, using, or selling the invention throughout the United States.”⁸ Except as otherwise provided, “whoever without authority makes, uses or sells any patented invention, within the United States during the term of the patent therefor, infringes the patent.”⁹ The parties agree that the 1984 Act was designed to respond to two unintended distortions of the 17-year patent term produced by the requirement that certain products must receive premarket regulatory approval. First, the holder of a patent relating to such products would as a practical matter not be able to reap any financial rewards during the early years of the term. When an inventor makes a potentially useful discovery, he ordinarily protects it by applying for a patent at once. Thus, if the discovery relates to a product that cannot be marketed without substantial testing and regulatory approval, the “clock” on his patent term will be running even though he is not yet able to derive any profit from the invention.

The second distortion occurred at the other end of the patent term. In 1984, the Court of Appeals for the Federal Circuit decided that the manufacture, use, or sale of a patented invention during the term of the patent constituted an act of infringement, see § 271(a), even if it was for the sole purpose of conducting tests and developing information necessary to apply for regulatory approval. *See*¹⁰ Since that activity could not be commenced by those who planned to compete with the patentee until expiration of the entire patent term, the patentee’s *de facto* monopoly would continue for an often substantial period until regulatory approval was obtained. In other words, the combined effect of the patent law and the premarket regulatory approval requirement was to create an effective extension of the patent term.

The Drug Price Competition and Patent Term Restoration Act of 1984¹¹ sought to eliminate this distortion from both ends of the patent

4. As amended at 21 U.S.C § 301 *eq seq.*

5. 21 U. S. C. § 355(i)(1)(A);

6. 21 U.S.C. § 355(b)(1)

7. Now twenty years.

8. 35 U.S.C. § 154.

9. 35 U.S.C. § 271(a)

10. *Roche Prods., Inc. v. Bolar Pharm. Co.*, 733 F.2d 858 (Fed. Cir. 1984).

11. Informally known as Hatch-Waxman, after its Congressional champions

period. Section 201 of the Act established a patent-term extension for patents relating to certain products that were subject to lengthy regulatory delays and could not be marketed prior to regulatory approval. The eligible products were described as follows:

- (1) The term ‘product’ means:
 - (A) A human drug product.
 - (B) Any medical device, food additive, or color additive subject to regulation under the Federal Food, Drug, and Cosmetic Act.
- (2) The term ‘human drug product’ means the active ingredient of –
 - (A) a new drug, antibiotic drug, or human biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act), or
 - (B) a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Virus-Serum-Toxin Act) ...¹²

Section 201 provides that patents relating to these products can be extended up to five years if, *inter alia*, the product was “subject to a regulatory review period before its commercial marketing or use,” and “the permission for the commercial marketing or use of the product after such regulatory review period [was] the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred.”

The distortion at the other end of the patent period was addressed by § 202 of the Act. That added to the provision prohibiting patent infringement¹³, the paragraph at issue here, establishing that “it shall not be an act of infringement to make, use, or sell a patented invention ... solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs.” This allows competitors, prior to the expiration of a patent, to engage in otherwise infringing activities necessary to obtain regulatory approval.

[The Court held that § 271(e) applies only to the FDA’s drug-approval process, and not to the non-drug provisions of federal laws that also happen to regulate drugs in some way. *Merck KGaA v. Integra Lifesciences I, Ltd.* is to similar effect: § 271(e) protects “uses of patented inventions in preclinical research, the results of which are not ultimately included in a submission to the FDA.”¹⁴]

2 Hatch-Waxman

A firm that develops a new (or “pioneer”) drug has a regulatory advantage: following approval of its NDA, no other firm is legally allowed to market the drug. A generic firm could of course submit its own NDA. This would probably be faster and cheaper than the pioneer firm’s NDA: after all, it would know what drug to test and write up. But it would still be slow and expensive, because it would require a full

12. 35 U.S.C. § 156(f) (2016). NB: the language has been amended since *Eli Lilly &*; this is the current version.

13. 35 U.S.C. § 271(e)(1)

14. *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193 (2005).

course of clinical testing and regulatory filing. So some firms tried to argue that generic drugs required no new approval from the FDA. In *United States v. Generix Drug Corp.*, the Supreme Court disagreed, holding that generic drugs “are quite plainly drugs within the meaning of the FDCA.”¹⁵ So the baseline remained that a generic drug requires a full NDA of its own.

In 1984, Congress enacted a grand bargain between pioneer and generic firms, commonly known as Hatch-Waxman for the names of its sponsors, that alters this baseline in several important ways:

1. It gives generic firms the option of filing an “abbreviated” NDA, or ANDA, in place of a full NDA based on new clinical trials.
2. It then prohibits the FDA from approving ANDAs during certain statutory exclusivity periods.
3. It creates specialized procedures to sort out conflicting claims over patents potentially reading on generic drugs.
4. Finally, it gives a limited form of exclusivity to generic drug firms who successfully challenge patents: 180 days during which no other ANDA can be approved for the same product.

Take these up in order.

Abbreviated NDAs

First, *FTC v. Actavis, Inc.* summarizes the ANDA process:

A drug manufacturer, wishing to market a new prescription drug, must submit a New Drug Application to the federal Food and Drug Administration and undergo a long, comprehensive, and costly testing process, after which, if successful, the manufacturer will receive marketing approval from the FDA. See 21 U.S.C. § 355(b)(1) (requiring, among other things, “full reports of investigations” into safety and effectiveness; “a full list of the articles used as components”; and a “full description” of how the drug is manufactured, processed, and packed).

Once the FDA has approved a brand-name drug for marketing, a manufacturer of a generic drug can obtain similar marketing approval through use of abbreviated procedures. The Hatch-Waxman Act permits a generic manufacturer to file an Abbreviated New Drug Application specifying that the generic has the same active ingredients as and is biologically equivalent to, the already-approved brand-name drug. In this way the generic manufacturer can obtain approval while avoiding the costly and time-consuming studies needed to obtain approval for a pioneer drug. The Hatch-Waxman process, by allowing the generic to piggyback on the pioneer’s approval efforts, speeds the introduction of low-cost generic drugs to market, thereby furthering drug competition.¹⁶

15. *United States v. Generix Drug Corp.*, 460 U.S. 453 (1983).

16. *FTC v. Actavis, Inc.*, 133 S. Ct. 2223 (2013).

Statutory Exclusivity

Second, *Actavis Elizabeth LLC v. U.S. Food & Drug Admin.* summarizes the statutory exclusivity periods during which the FDA may not approve ANDAs:

The exclusivity provisions protect these drugs from generic competition for the specified terms by preventing the submission of abbreviated applications that refer to them.

If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved after September 24, 1984, no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the approval ...¹⁷

In addition to this five-year period, the Amendments grant three-year exclusivity to drugs that include previously approved active ingredients if the application for the drug “contains¹⁸. reports of new clinical investigations ... essential to the approval of the application and conducted or sponsored by the applicant.”¹⁹

The FDA has implemented these exclusivity provisions through regulations. The regulations give five years of exclusivity for each “drug product that contains a new chemical entity.”²⁰ A “new chemical entity” is “a drug that contains no active moiety that has been approved by FDA in any other” new drug application. “Active moiety” is defined as “the molecule or ion ... responsible for the physiological or pharmacological action of the drug substance.”²¹

Health-law scholar Erika Lietzan argues that we should think of these statutory periods as *data* exclusivity (“prohibitions on submission or approval of *abbreviated* applications, which implicitly or explicitly rely on previously submitted data”) rather than *market* exclusivity (“prohibitions on submission or approval of any competing application, even if supported by a full complement of original data.”).²²

The conventional narrative indicates that data exclusivity is *affirmatively* provided by the state—the subtext being that the natural state of affairs is one *without* data exclusivity. Many legal scholars and policy writers describe data exclusivity as comparable to intellectual property, as patent-like, or even as a sub-type of intellectual property. The innovative industry also tends to characterize it as a type of intellectual property. Both economic and legal scholars analogize to

17. 21 U.S.C § 355(j)(5)(f)(ii)

18. 21 U.S.C. § 355(j)(5)(F)(iii)

19. The Best Pharmaceuticals for Children Act gives six months of additional exclusivity if the applicant conducts certain require forms of pediatric testing. See 21 U.S.C. § 355a.

20. 21 C.F.R. § 314.108(a) & (b)(2)

21. *Actavis Elizabeth LLC v. U.S. Food & Drug Admin.*, 625 F.3d 760 (D.C. Cir. 2010).

22. Erika Lietzan, *The Myths of Data Exclusivity*, 20 LEWIS & CLARK L. REV. 91 (2016).

monopoly when describing market conditions during data exclusivity – the subtext again being that natural competition has been affirmatively blocked by the State. The key to the conventional narrative is that exclusivity is artificial and provided, as a benefit, to pioneers.

But there is another way to understand what is going on. The government requires a license to market new drugs, which it will issue after reviewing the results of research to support the marketability of the drug. Anyone may apply for a license, and indeed – subject to any relevant patent protection one or another of the companies might enjoy as well as their business judgment about the value of the investment – multiple companies may file for licenses to market the same drug or drugs that are similar. That is to say, the drug approval statutes – the regulatory apparatuses – do not preclude two, or three or more applicants from seeking approval of the same thing on the same terms. From a regulatory perspective, all face the same scientific burden – preclinical and clinical research in a full application, showing the finished product is safe and effective. The second and third applicant will have a reduced burden as a practical matter simply because approval of the first product – and the large volume of information released about the contents of the application – will eliminate much of the trial and error that the first applicant experienced. They will know what to study and what not to study, they will know how to design their trials, they will know what results to expect, and they can reverse engineer the first entrant’s product to determine a suitable formulation, route of administration, dosage form, and strength. All of this will save these applicants *some* time and money, but the bulk of their expenses remain, deriving from the clinical trials that must still be performed to obtain a license.²³

After a period of time, federal law permits other companies to obtain licenses for identical or highly similar medicines *without* the same amount of supporting research. The drug approval statutes remove the high evidentiary hurdle and substitute a different one, with a significantly lower investment requirement. A license to market is now available for the price of comparative analytical testing and perhaps modest comparative clinical testing. As a scientific matter, these follow-on applicants are able to obtain licenses because they rely on the research performed by the earlier applicant. That these are reliance-based applications should not be controversial.²⁴ FDA has conceded that as a regulatory matter a follow-on applicant uses the first entrant’s research, even if sometimes couching it as using the “fact” of the first entrant’s approval. Many courts charac-

23. What does the FDA’s new drug approval process look like from a trade-secret point of view? Does this help explain the term “data exclusivity?”
24. Drug approval isn’t the only case of data exclusivity in federal law. For example, the Federal Insecticide, Fungicide, and Rodenticide Act, which is understandably concerned with the safety of chemicals being used for their toxic qualities, has its own data exclusivity regime administered by the EPA.

generic drug approval use the same language. In brief, then, once data exclusivity expires, any applicant may justify market entry using the research paid for and submitted by the pioneer to justify its own entry to the market. This reframes data exclusivity as a period before the law gives the pioneer's competitors something not previously available to them – a faster and cheaper license, resulting from permission to rely on the pioneer's research.

When the narrative is recast, the central myth of exclusivity is exposed; it is not a grant of anything to anyone. Data exclusivity is the *absence* of an abbreviated pathway. It does not prevent subsequent entrants from doing exactly what the first entrant did—developing the product, testing it, submitting a full application, and launching the drug, subject to relevant patent and business considerations. Contrasting *data* exclusivity with *market* exclusivity should make this clear.

Orphan-drug exclusivity is the main example in current U.S. law of market exclusivity. An orphan drug is intended to treat a rare disease or condition; the sponsor makes this showing by demonstrating that the disease affects fewer than 200,000 persons in this country or that the company does not expect to recover its costs of research and development when marketing the product. If a drug has been designated as an orphan drug, then – upon approval – it is entitled to seven years of market exclusivity. This means the FDA may not approve the same drug for the same condition for seven years, even if proposed in a full application supported by original research. Orphan-drug exclusivity is an affirmatively granted right, in the sense that it prevents subsequent entrants from doing what they would ordinarily and otherwise be permitted to do – study the molecule themselves and reach the market on the same terms as the first entrant.²⁵

25. Lietzan, *supra* note 22.

The Orange Book

Caraco Pharmaceutical Labs v. Novo Nordisk summarizes the elaborate quadrille between a pioneer patent owner, a generic entrant, the FDA, and the courts for sorting out ANDA approval for drugs covered by patents:

Because the FDA cannot authorize a generic drug that would infringe a patent, the timing of an ANDA's approval depends on the scope and duration of the patents covering the brand-name drug. Those patents come in different varieties. One type protects the drug compound itself. Another kind – the one at issue here – gives the brand manufacturer exclusive rights over a particular method of using the drug. In some circumstances, a brand manufacturer may hold such a method-of-use patent even after its patent on the drug com-

pound has expired.

To facilitate the approval of generic drugs as soon as patents allow, the Hatch-Waxman Amendments and FDA regulations direct brand manufacturers to file information about their patents. The statute mandates that a brand submit in its NDA "the patent number²⁶ and the expiration date of any patent which claims the drug for which the [brand] submitted the [NDA] or which claims a method of using such drug." And the regulations issued under that statute require that, once an NDA is approved, the brand provide a description of any method-of-use patent it holds. That description is known as a use code, and the brand submits it on FDA Form 3542. As later discussed, the FDA does not attempt to verify the accuracy of the use codes that brand manufacturers supply. It simply publishes the codes, along with the corresponding patent numbers and expiration dates, in a fat, brightly hued volume called the Orange Book (less colorfully but more officially denominated Approved Drug Products with Therapeutic Equivalence Evaluations).

26. 21 U.S.C. §§ 355(b)(1)

After consulting the Orange Book, a company filing an ANDA must assure the FDA that its proposed generic drug will not infringe the brand's patents. When no patents are listed in the Orange Book or all listed patents have expired (or will expire prior to the ANDA's approval), the generic manufacturer simply certifies to that effect. Otherwise, the applicant has two possible ways to obtain approval.

One option is to submit a so-called section viii statement, which asserts that the generic manufacturer will market the drug for one or more methods of use not covered by the brand's patents. A section viii statement is typically used when the brand's patent on the drug compound has expired and the brand holds patents on only some approved methods of using the drug. If the ANDA applicant follows this route, it will propose labeling for the generic drug that "carves out" from the brand's approved label the still-patented methods of use. The FDA may approve such a modified label as an exception to the usual rule that a generic drug must bear the same label as the brand-name product. FDA acceptance of the carve-out label allows the generic company to place its drug on the market (assuming the ANDA meets other requirements), but only for a subset of approved uses – i.e., those not covered by the brand's patents.

Of particular relevance here, the FDA will not approve such an ANDA if the generic's proposed carve-out label overlaps at all with the brand's use code. The FDA takes that code as a given: It does not independently assess the patent's scope or otherwise look behind the description au-

thored by the brand. According to the agency, it lacks “both the expertise and the authority” to review patent claims; although it will forward questions about the accuracy of a use code to the brand, its own “role with respect to patent listing is ministerial.” Thus, whether section viii is available to a generic manufacturer depends on how the brand describes its patent. Only if the use code provides sufficient space for the generic’s proposed label will the FDA approve an ANDA with a section viii statement.

The generic manufacturer’s second option is to file a so-called paragraph IV certification, which states that a listed patent “is invalid or will not be infringed by the manufacture, use, or sale of the [generic] drug.”²⁷ A generic manufacturer will typically take this path in either of two situations: if it wants to market the drug for all uses, rather than carving out those still allegedly under patent; or if it discovers, as described above, that any carve-out label it is willing to adopt cannot avoid the brand’s use code. Filing a paragraph IV certification means provoking litigation. The patent statute treats such a filing as itself an act of infringement, which gives the brand an immediate right to sue.²⁸ Assuming the brand does so, the FDA generally may not approve the ANDA until 30 months pass or the court finds the patent invalid or not infringed. Accordingly, the paragraph IV process is likely to keep the generic drug off the market for a lengthy period, but may eventually enable the generic company to market its drug for all approved uses.

In the late 1990’s, evidence mounted that some brands were exploiting this statutory scheme to prevent or delay the marketing of generic drugs, and the Federal Trade Commission (FTC) soon issued a study detailing these anticompetitive practices. That report focused attention on brands’ submission of inaccurate patent information to the FDA. In one case cited by the FTC,²⁹ a brand whose original patent on a drug was set to expire listed a new patent ostensibly extending its rights over the drug, but in fact covering neither the compound nor any method of using it. The FDA, as was (and is) its wont, accepted the listing at its word and accordingly declined to approve a generic product. The generic manufacturer sued to delete the improper listing from the Orange Book, but the Federal Circuit held that the Hatch-Waxman Amendments did not allow such a right of action. As the FTC noted, that ruling meant that the only option for generic manufacturers in Mylan’s situation was to file a paragraph IV certification (triggering an infringement suit) and then wait out the usual 30-month period before the FDA could approve an ANDA.

Congress responded to these abuses by creating a mech-

27. 21 U.S.C. S 355(j)(2)(A)(vii)(IV)

28. 35 U.S.C. S 271(e)(2)(A)

29. Mylan Pharm., Inc. v. Thompson, 268 F.3d 1323 (Fed. Cir. 2001).

anism, in the form of a legal counterclaim, for generic manufacturers to challenge patent information a brand has submitted to the FDA. The provision authorizes an ANDA applicant sued for patent infringement to “assert a counterclaim³⁰ seeking an order requiring the [brand] to correct or delete the patent information submitted by the [brand] under subsection (b) or (c) [of S 355] on the ground that the patent does not claim either (aa) the drug for which the [brand’s NDA] was approved; or (bb) an approved method of using the drug.”

The counterclaim thus enables a generic competitor to obtain a judgment directing a brand to “correct or delete” certain patent information that is blocking the FDA’s approval of a generic product. This case raises the question whether the counterclaim is available to fix a brand’s use code.³¹

The text and context of the provision demonstrate that a generic company can employ the counterclaim to challenge a brand’s overbroad use code. The Hatch-Waxman Amendments authorize the FDA to approve the marketing of a generic drug for particular unpatented uses; and section viii provides the mechanism for a generic company to identify those uses, so that a product with a label matching them can quickly come to market. The statutory scheme, in other words, contemplates that one patented use will not foreclose marketing a generic drug for other unpatented ones. Within that framework, the counterclaim naturally functions to challenge the brand’s assertion of rights over whichever discrete use (or uses) the generic company wishes to pursue. That assertion, after all, is the thing blocking the generic drug’s entry on the market. The availability of the counterclaim thus matches the availability of FDA approval under the statute: A company may bring a counterclaim to show that a method of use is unpatented because establishing that fact allows the FDA to authorize a generic drug via section viii.³²

Generic Exclusivity

Finally, Hatch-Waxman provides a reward for a generic entrant that successfully challenges the validity of a patent on an approved drug. *FTC v. Actavis, Inc.* explains:

The Hatch-Waxman Act requires the generic manufacturer in its Abbreviated New Drug Application to “assure the FDA” that the generic “will not infringe” the brand-name’s patents. The generic can provide this assurance in one of several ways.³³ It can certify that the brand-name manufacturer has not listed any relevant patents. It can certify that

30. 21 U.S.C. S 355(j)(5)(C)(ii)(I)

31. Justice Kagan’s statutory construction discussion makes for entertaining reading but would take us too far afield. Here’s a sample: “‘Not an’ sometimes means ‘not any,’ in the way Novo claims. If your spouse tells you he is late because he ‘did not take a cab,’ you will infer that he took no cab at all (but took the bus instead). But now stop a moment. Suppose your spouse tells you that he got lost because he ‘did not make a turn.’ You would understand that he failed to make a particular turn, not that he drove from the outset in a straight line.”

32. *Caraco Pharm. Labs v. Novo Nordisk*, 132 S. Ct. 1670 (2012).

33. 21 U.S.C. § 355(j)(2)(A)(vii)

any relevant patents have expired. It can request approval to market beginning when any still-in-force patents expire. Or, it can certify that any listed, relevant patent "is invalid or will not be infringed by the manufacture, use, or sale" of the drug described in the Abbreviated New Drug Application. Taking this last-mentioned route (called the "paragraph IV" route), automatically counts as patent infringement,³⁴ and often means provoking litigation. If the brand-name patentee brings an infringement suit within 45 days, the FDA then must withhold approving the generic, usually for a 30-month period, while the parties litigate patent validity (or infringement) in court. If the courts decide the matter within that period, the FDA follows that determination; if they do not, the FDA may go forward and give approval to market the generic product.

34. 35 U.S.C. § 271(e)(2)(A)

Hatch-Waxman provides a special incentive for a generic to be the first to file an ANDA taking the paragraph IV route. That applicant will enjoy a period of 180 days of exclusivity (from the first commercial marketing of its drug).³⁵ During that period of exclusivity no other generic can compete with the brand-name drug. If the first-to-file generic manufacturer can overcome any patent obstacle and bring the generic to market, this 180-day period of exclusivity can prove valuable, possibly worth several hundred million dollars. Indeed, the Generic Pharmaceutical Association said in 2006 that the "vast majority of potential profits for a generic drug manufacturer materialize during the 180-day exclusivity period." The 180-day exclusivity period, however, can belong only to the first generic to file. Should that first-to-file generic forfeit the exclusivity right in one of the ways specified by statute, no other generic can obtain it.³⁶

35. 21 U.S.C § 355(j)(5)(B)(iv)

36. *FTC v. Actavis, Inc.*, 133 S.Ct. 2223 (2013).

This is quite a complicated scheme. Take a moment to see if you can figure out how it could be gamed before reading on. When you are ready, look at this excerpt from *Actavis*:

Company A sues Company B for patent infringement. The two companies settle under terms that require (1) Company B, the claimed infringer, not to produce the patented product until the patent's term expires, and (2) Company A, the patentee, to pay B many millions of dollars. Because the settlement requires the patentee to pay the alleged infringer, rather than the other way around, this kind of settlement agreement is often called a "reverse payment" settlement agreement. . . .

Apparently most if not all reverse payment settlement agreements arise in the context of pharmaceutical drug regulation, and specifically in the context of suits brought under statutory provisions allowing a generic drug manufacturer

(seeking speedy marketing approval [under an ANDA]) to challenge the validity of a patent owned by an already-approved brand-name drug owner. . . .

But, one might ask, as a practical matter would the parties be able to enter into such an anticompetitive agreement? Would not a high reverse payment signal to other potential challengers that the patentee lacks confidence in its patent, thereby provoking additional challenges, perhaps too many for the patentee to “buy off?” Two special features of Hatch-Waxman mean that the answer to this question is “not necessarily so.” First, under Hatch-Waxman only the first challenger gains the special advantage of 180 days of an exclusive right to sell a generic version of the brand-name product. And as noted, that right has proved valuable – indeed, it can be worth several hundred million dollars. Subsequent challengers cannot secure that exclusivity period, and thus stand to win significantly less than the first if they bring a successful paragraph IV challenge. That is, if subsequent litigation results in invalidation of the patent, or a ruling that the patent is not infringed, that litigation victory will free not just the challenger to compete, but all other potential competitors too (once they obtain FDA approval). The potential reward available to a subsequent challenger being significantly less, the patentee’s payment to the initial challenger (in return for not pressing the patent challenge) will not necessarily provoke subsequent challenges. Second, a generic that files a paragraph IV after learning that the first filer has settled will (if sued by the brand-name) have to wait out a stay period of (roughly) 30 months before the FDA may approve its application, just as the first filer did. These features together mean that a reverse payment settlement with the first filer removes from consideration the most motivated challenger, and the one closest to introducing competition. It may well be that Hatch-Waxman’s unique regulatory framework, including the special advantage that the 180-day exclusivity period gives to first filers, does much to explain why in this context, but not others, the patentee’s ordinary incentives to resist paying off challengers (i.e., the fear of provoking myriad other challengers) appear to be more frequently overcome.³⁷

37. *Id.*

The Court held that these reverse settlements could violate the antitrust laws.

3 Orphan Drugs

Lietzan contrasts the “data exclusivity” granted to pioneer drugs to the “market exclusivity” granted to orphan drugs. This section considers the orphan-drug exclusivity in more detail. Because it prohibits any

subsequent NDA, it is in effect a true IP regime that gives patent-like protection for the only economically significant use of a product. This summary is from *Genentech, Inc. v. Bowen*:

As food and drug regulatory statutes go, the Orphan Drug Act is relatively straightforward and politically uncontroversial. A pharmaceutical company often must spend \$80 million or more to develop a single new drug. When the potential market for a drug is small – because the number of persons afflicted with the particular disease or condition which the drug treats is relatively small – it may be impossible for the manufacturer to recover its sizable research and development investment, much less realize an acceptable return on that investment. The Act is designed to combat the general unwillingness of pharmaceutical manufacturers to invest in the development of commercial drugs for the treatment of diseases which, although devastating to their victims, afflict too small a proportion of the population to make them commercially viable.

The Act seeks to encourage the development of “orphan drugs” by reducing the overall financial cost of development, while enhancing the developer’s ability to recover that cost through sale of the drug. Specifically, the Act attempts to reduce development costs by streamlining the FDA’s approval process for orphan drugs, by providing tax breaks for expenses related to orphan drug development,[by authorizing the FDA to assist in funding the clinical testing necessary for approval of an orphan drug, and by creating an Orphan Products Board to coordinate public and private development efforts. The Act seeks to enhance the orphan drug manufacturer’s ability to recover his investment by granting the manufacturer seven years of exclusive marketing rights “for such drug for such [rare] disease or condition.” A “rare disease or condition” is one which “affects less than 200,000 persons in the United States,”³⁸ or one which “affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug.”

Qualification for orphan drug benefits occurs in a two-step process. At any phase of the research and development process, a manufacturer who believes its drug will treat a “rare disease or condition” may apply to the FDA for designation as “a drug for a rare disease or condition.” Although the Act does not limit the number of drugs that may be designated for treatment of a particular rare disease the FDA’s present policy is to not consider requests for orphan drug

38. 21 U.S.C. § 360bb

designation made after that drug has received full FDA marketing approval for that particular disease.

While any number of drugs may receive the development-phase benefits of the Act, only one manufacturer may receive exclusive marketing rights. This post-development benefit is reserved for the first manufacturer to receive full FDA approval of its drug as safe and effective for commercial sale.

If the FDA ... approves an application³⁹ ... for a drug designated under section 360bb of this title for a rare disease or condition, the FDA may not approve another application ... for such drug for such disease or condition for a person who is not the holder of such approved application ... until the expiration of seven years from the date of approval of the approved application. ...

39. 21 U.S.C. § 360cc(a)

The FDA may authorize another manufacturer to produce "such drug for such disease or condition" only if the exclusive marketer consents in writing or is incapable of providing sufficient quantities of the drug.

As originally enacted, the Act limited the availability of exclusive marketing rights to drugs "for which a United States Letter of Patent may not be issued...." In considering the proposed legislation, the House Committee on Energy and Commerce found that many potential orphan drugs are not patentable, and stated: "In order to provide some incentive for the development of these particular orphan drugs, the Committee's bill includes an exclusive marketing right for the sponsor of such a drug." Thus, the exclusivity provision of the Act was designed to complement the patent laws, filling gaps which might leave orphan drug manufacturers unprotected.

In 1985, Congress amended the Act to delete the non-patentability criterion in the exclusivity provision. The Committee's expectation when it drafted the original provision in 1983 had been that exclusivity would be used primarily by orphan drugs that could not get product patents. However, experience under the Act demonstrated that reliance on the incentives of patent protection for all patentable orphan drugs would be insufficient. First, many patents expire before completion of the clinical testing necessary for FDA marketing approval. Second, in many cases the product patent on a drug is held by an individual or company other than the one that intends to test the drug for use against a rare disease, and prior academic publication in the area precludes issuance of a use patent. Accordingly, the fact that a product patent has been issued does not always ensure that

a manufacturer will have a sufficient incentive to apply for permission to market the drug as an orphan drug.

In expanding the exclusivity provision to cover both patented and unpatented orphan drugs, the Committee noted that the provision would only benefit the sponsors of drugs with less than seven years of product patent protection available, and explained the difference between exclusivity under the Act and traditional patent protection. First, traditional patents generally offer much broader protection than orphan drug exclusivity, which is limited to treatment of a particular disease. Second, while the inviolability of a patent is limited only by the holder's ability to enforce his rights in court, orphan drug exclusivity exists only so long as the sponsor adequately supplies the market.

The Committee expressed its desire that elimination of the patentability distinction, while probably still not making orphan drugs profitable business ventures, would strengthen development by providing greater certainty to potential orphan drug sponsors.⁴⁰

Orphan-exclusivity is "per-disease," not "per-drug." The FDA can and does grant orphan exclusivity to a drug for one use, while leaving other uses uncovered. Consider, for example, *Sigma-Tau Pharmaceuticals, Inc. v. Schwetz*, in which Sigma-Tau developed a levocarnitine drug, which it marketed as Carnitor, for the treatment of carnitine deficiency in patients with inborn metabolic disorders ("IMD").⁴¹ It received FDA approval and orphan-drug status for IMD carnitine deficiency; its exclusivity expired in 1999.

Sigma-Tau then received FDA approval and orphan-drug status for a second use of Carnitor: treating carnitine deficiency in patients with end-stage renal disease (ESRD). Two generic drug manufacturers applied for and received FDA approval to sell generic versions of Carnitor for treatment of IMD. Sigma-Tau sued, but the court held that the FDA had acted properly. Sigma-Tau had exclusivity only for the treatment of ESRD, not IMD.

That said, Sigma-Tau's lawsuit got at a serious point about the drug-prescribing system in the United States:

Sigma-Tau contends that the FDA was obligated to look beyond the labeling to what Sigma-Tau maintains is the reality of the situation, which is that most of the need for the generics – and thus most of the money to be made – lies in treating patients with ESRD.⁴²

Once a drug can be legally sold *at all*, physicians are allowed to administer it for *any* use they in their professional judgment consider appropriate for their patients. The drug can only be marketed for the approved uses, and these uses are listed on the *label* with detailed drug information that the FDA approves when it approves an NDA – physicians

40. *Genentech, Inc. v. Bowen*, 676 F. Supp. 301 (D.D.C. 1987).

41. *Sigma-Tau Pharm., Inc. v. Schwetz*, 288 F.3d 141 (4th Cir. 2002).

42. *Id.*

can engage in *off-label* uses that go beyond the approved ones. For the *Sigma-Tau Pharmaceuticals* court, the possibility of off-label uses was a reason to approve of the FDA's decision:

As the district court noted, not only might this course of events result in extensions of exclusivity periods that Congress never intended, but it also might frustrate the long-standing practice of Congress, the FDA, and the courts not to interfere with physicians' judgments and their prescription of drugs for off-label uses. In light of the ensuing effects on the delivery of health care and drug prices in this country, such interference with off-label use is not something we would be wise to welcome, let alone help to bring about. Even Sigma-Tau appears to agree that the medical community's foreseeable off-label use of drugs does not violate the ODA.⁴³

43. *Id.*

B Marketing

Even after approval, the regulatory regime for drugs creates interesting intellectual property issues because the *marketing* of drugs is heavily restricted. We focus on issues relating to drugs' names, physical design, and advertising.

1 Names

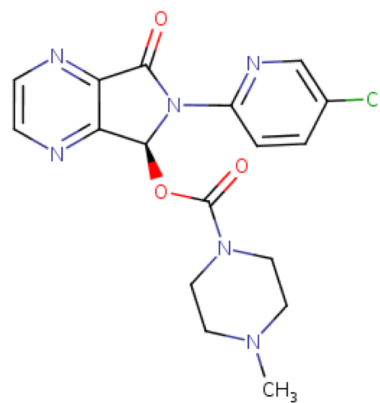
Trademark law regulates drug names to prevent confusion. But it is not the only body of law that does so: the FDA also limits what drug makers can and cannot call their drugs.

Drug names are trademarks, right? So trademark law applies? Yes, but.

Any given drug typically has numerous names. (To illustrate, we'll focus on drugs with a single active ingredient.) Consider as an example the chemical with the molecular structure shown in the margin. According to the *Nomenclature of Organic Chemistry*, a 1600-page guide published and regularly revised by the International Union of Pure and Applied Chemists, the preferred IUPAC name of this molecule is [(7S)-6-(5-chloropyridin-2-yl)-5-oxo-7H-pyrrolo[3,4-b]pyrazin-7-yl] 4-methylpiperazine-1-carboxylate. This is close to useless as a drug name; neither doctors nor patients are going to be able to remember all of that.

Instead, humans have given the molecule an *adopted name* (also called a "nonproprietary name"): *eszopiclone*. Adopted names for drugs are assigned by the United States Adopted Names Council. It works with applicants – typically companies considering manufacturing drugs – to devise appropriate adopted names according to a detailed **list of criteria**. Here are a few of the principles:

1. A nonproprietary name should be useful primarily to health care



Eszopiclone

practitioners, especially physicians, pharmacists, nurses, educators, dentists and veterinarians.

- 2.a The name for the active moiety of a drug should be a single word, preferably with no more than four syllables.
- 3.a A common, simple word element (a "stem") should be incorporated in the names of all members of a group of related drugs when pertinent, common characteristics can be identified, such as similarity of pharmacological action.⁴⁴
4. A name should be free from conflict with other nonproprietary names and with established trademarks and should be neither confusing nor misleading. ...
 1. Prefixes that imply "better," "newer" or "more effective;" prefixes that evoke the name of the sponsor, dosage form, duration of action or rate of drug release should not be used. Examples include "dura," "forte," or "efex."

Adopted names chosen this way are partly descriptive (look at those stems) and partly coined (look at the list of things the names may not describe).⁴⁵ The FDA considers some names to be *established names* for drugs⁴⁶ – or, informally, the "generic name," because it generally functions as a generic name in the trademark law sense. The distinction between an adopted name and an established name is simply that the latter has the FDA's sanction as "the" generic name, not just "a" generic name. (As we will see in a moment, the FDA requires drugmakers to list the established name of their products, even when they also use a trademark). Where the USAN Council has selected an assigned name, the FDA will treat it as the established name, so the established name of this drug is also *eszopiclone*. But not all established names come through the USAN Council. Some drugs have "common names": i.e., the names that have come to be used generically by the public to refer to the drug, of which *aspirin* is an example.

And now back to trademarks. When a drugmaker submits an application to the FDA, it must also list the proprietary name it proposes to market the drug under.⁴⁷ The FDA then engages in an extensive substantive examination of the name designed to minimize errors by medical professionals and patients. Under its [Contents of a Complete Submission for the Evaluation of Proprietary Names](#) (2016) and [Best Practices in Developing Proprietary Names for Drugs](#) (draft 2014), the FDA will, for example:

- Require that the proprietary name be different from the established name. Indeed, the proprietary name may *not* incorporate USAN stems at all.
- Reject proposed proprietary names that are confusingly similar to other proprietary names, established names, or ingredient names. This is a much more searching inquiry than the trademark likelihood of confusion analysis. The FDA will compare the proposed name against its Phonetic and Orthographic Computer Analysis

44. For example, the stem *-clone* indicates a hypnotic tranquilizer, the stem *-cog* is used for blood coagulation factors, and the stem *-conazole* describes an antifungal agent.

45. Here is the USAN Council's [statement on eszopiclone](#).

46. See 21 C.F.R. § 299.4

47. Are the following the names of drugs or of elves?

- Frova
- Erester
- Isentress
- Qvar
- Celeborn
- Oropher

See [Which Is It: Prescription Drug or Tolkien Elf?](#) at How Stuff Works: Entertainment

system for look-alike and sound-alike combinations, and also conduct or require "simulation studies":

Name simulation tests should reflect the full range and variety of tasks involved in the prescribing, transcribing, dispensing, and administration of drugs, as well as tasks involved in consumer selection of OTC drugs. Simulations should include common and easily simulated characteristics of real use, such as using ruled or unruled paper, prescription pads, computer order entry, and telephone orders to approximate written, oral, and electronic prescribing in the setting of care for the proposed product (e.g., inpatient and outpatient settings, long-term care). Simulations also should approximate the diversity of real-world prescribing conditions by varying factors such as background noise, handwriting samples, different ink colors, directions for use, and different voices/accents. In addition, the simulation study should present the proprietary name with the corresponding product characteristics (e.g., strength, route, dosage, and frequency) that are likely to be used to communicate prescriptions and orders for the proposed product.

- Prevent the use of the same proprietary name on products with different active ingredients.
- Reject a proposed proprietary name that could "result in ... misbranding if it is false or misleading, such as by making misrepresentations with respect to safety or efficacy." The FDA elaborates:

For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not. For example, FDA likely would object to a proposed proprietary name that contained the prefix *best* or that sounds like *best* because it implies superiority over other currently available therapies. In the absence of appropriate scientific evidence to support claims that the product is superior to other competing products currently on the market to treat the condition, such a proposed name would be misleading.

Note that this review is separate and apart from the USPTO's review of a trademark application. This is true on the back end as well as the front end: someone proposing to sell a competing branded version of the same drug will need to get its name through the FDA's approval process, not just past the trademark standard. The result – as you can probably guess by now – is that the FDA's rigorous standards for proprietary names in effect create a special and distinctive trademark system for branded drugs. Here, our molecule is sold under the proprietary

name LUNESTA for the treatment of insomnia. The brand name doesn't directly say that it works as a sleep aid, but it certainly suggests certain appealing characteristics of one.

FDA regulations require that drug labels and packaging bear the established name, "in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined."⁴⁸

For an illustration of the interaction between the drug-approval system and trademark law, consider *Kos Pharmaceuticals, Inc. v. Andrx Corp.*⁴⁹ Kos sold a drug consisting of a combination of lovastatin and niacin as a medication to improve cholesterol levels under the name AVIDCOR. Andrx announced plans to sell its own cholesterol medication, containing only niacin, as ALTOCOR. Andrx applied to the FDA for approval of the drug and to the USPTO to register ALTOCOR as a trademark. Kos opposed it in both forums, and also sued for trademark infringement. The court granted a preliminary injunction. Here is its discussion of the relevant types of confusion:

The District Court used an overly narrow definition of confusion, in effect evaluating the likelihood of *misdispensing* rather than *confusion*. Andrx also claims that "the FDA and the USPTO have determined that the marks are not confusingly similar." But neither of those proceedings can supplant the required Lanham Act analysis. First, the FDA applies a standard different from the Lanham Act "likelihood of confusion" test at issue here. The FDA reviews proposed drug names to predict potential confusion that may arise in the actual prescription process. Misdispensing is not the only type of confusion actionable under the Lanham Act. Indeed, to the extent that the FDA's proprietary name review is relevant here, the reviewing division's statement that the "name Advicor looks and sounds similar to Altocor" actually supports Kos's claim.

The facial similarity of the marks is apparent on their face. Both are seven-letter, three-syllable words that begin and end with the same letters and the same sounds. The marks are also similar in that both are coined words, not found even in approximation in the English or any other familiar language. Two names that look and sound similar will naturally seem even more similar where there are no differences in meaning to distinguish them. Nor can the similarity of coined marks be explained by, or ameliorated by virtue of, any relationship between the marks and the products identified.

The district court and the parties treated medical professionals, such as doctors, nurses and pharmacists, as the relevant consumers.¹² These trained professionals may be expected to be knowledgeable about, and to exercise care in

48. 21 C.F.R. § 201.10(g)(2).

49. *Kos Pharm., Inc. v. Andrx Corp.*, 369 F.3d 700 (3d Cir. 2004).

12. We note that neither the parties nor the court below addressed the possible confusion of ultimate consumers. While doctors and pharmacists play a gate-keeping role between patients and prescription drugs, they are not the ultimate consumers. Patients are. Courts have noted that drugs are increasingly marketed directly to potential patients through, for example, "ask-your-doctor-about-Brand-X" style advertising.

distinguishing between, medicines. We have emphasized a countervailing concern that weighs against allowing the expertise of physicians and pharmacists to trump other factors in assessing the likelihood of confusion in drug cases. Prevention of confusion and mistakes in medicines is too vital to be trifled with since confusion in such products can have serious consequences for the patient.

Andrx argues that confusion is even less likely here than in other cases involving medical professionals since prescriptions must reflect the different chemical composition of the drugs, with Advicor prescriptions specifying strengths of two active ingredients, and Altocor only one. Of course, this difference in prescribing is not relevant to the common practice of providing samples or to any type of confusion other than misdispensing. There is no reason to believe that medical expertise as to products will obviate confusion as to source or affiliation or other factors affecting goodwill.

Advicor and Altocor are both prescription drugs used to improve cholesterol levels. The products are of the same type and serve the same function in slightly different (but overlapping) ways that may be appropriate for slightly different (but overlapping) sets of patients. That doctors will need to decide which drug to prescribe does not mean they won't see the drugs as related or otherwise associate them. Indeed, it could be argued that the opposite is true, that is, that they will associate the products because they must consider both to decide which to prescribe.

The parties submitted competing medical affidavits to support their respective views as to the nature and severity of the potential consequences of a mis-filled prescription. Andrx also disputed Kos's allegations as to the risks of misdispensing by arguing it is extremely unlikely that a pharmacist would improperly fill a prescription. The district court resolved this dispute in Andrx's favor, holding that Kos had not proven that the public would face a serious health risk absent an injunction. The colloquy at the hearing shows that the court was impressed by the FDA's statement that the "possibility of confusion was minimal," and was persuaded that "it would be difficult to imagine a situation" where the drugs would be confused "when a pharmacist is filling a prescription." We note that, although the FDA's inquiry is not equivalent to the Lanham Act "likelihood of confusion" test, its review of proprietary drug names is relevant in assessing the health risks of mis-filled prescriptions. Indeed, the purpose of FDA review is to predict potential confusion that may arise in the actual prescription process. We defer to the district court's resolution of this factual dispute because its finding is supported by the record and is thus not clearly er-

roneous.

We must, however, distinguish between the court's finding that Kos did not establish a "serious health risk" and its conclusion that "therefore, the public interest does not favor" injunctive relief. While we defer to the former, the court's ultimate assessment of the public interest is clearly erroneous because it does not take into account the right of the public not to be deceived or confused.

2 Design

One might expect the law of drug trade dress to track the law of drug names closely. One would be wrong. For one thing, there is no review process for drug-format designs (like pill shapes and colors) that parallels the FDA's review of proprietary names to prevent misdispensing. For another, the courts are willing to hold that drug formats can be functional, because they allow patients and pharmacists to recognize generic substitutes for drugs as the "same" for dispensing purposes.

In *Shire US Inc. v. Barr Laboratories, Inc.*, for example, Shire sold the anti-ADHD stimulant Adderall in a series of tablets that corresponded to dosage:

The tablets are currently either blue or pale orange/peach and either round or oval. Color and size vary with the tablet's strength, seven of which currently are prescribed: 5 mg. (blue, round), 7.5 mg. (blue, oval), 10 mg. (blue, round), 12.5 mg. (orange/peach, round), 15 mg. (orange/peach, oval), 20 mg. (orange/peach, round), and 30 mg. (orange/peach, round). Adderall tablets are scored and stamped with the mark "AD" on one side and the dosage size, e.g., "10" on the other.⁵⁰

Barr sold a generic equivalent to Adderall under an ANDA. The products had equivalent active ingredients, but some of the other ingredients were different.

Barr's generic amphetamine salts are oval and convex in shape. Both the size and the color of Barr's tablets are linked to dosage. The face of the tablets has a "b" mark or the trade name Barr, and contains a numerical product code. The district court, on the basis of its physical examination of the tablets and the record before it, determined that while Barr's tablets, like Shire's, are blue and peach/light orange and those colors are keyed to dosage amounts, their shape and markings are different and "[j]uxtaposed against one another, the products are similar though not identical."⁵¹

Shire sued for trade dress infringement, and Barr defended on the grounds that the design of Adderall was functional. The court agreed, and its discussion of the indicia of functionality is illuminating:



Shire 20mg Adderall mixed amphetamine salts

50. *Shire US Inc. v. Barr Labs., Inc.*, 329 F.3d 348 (3d Cir. 2003).



Barr 20mg mixed amphetamine salts

51. *Id.*

Dr. Lawson F. Bernstein's declaration explains that because ADHD patients overuse visual cues, (1) when therapeutically equivalent ADHD products have similar visual recognition properties, adult ADHD patients will experience less confusion in correctly identifying the agent and/or its dosage strength; (2) given that almost all patients require some initial dosage titration and a subsequent substantial majority require intermittent dosage adjustment, the color coding of a particular preparation of mixed amphetamine salts tablets confers a substantial degree of clinical functionality for the patient in the titration/adjustment process; (3) many adult patients may take multiple daily dosages of different strength amphetamine salts tablets, also inferring the usefulness of similar color-coding.

Dr. Blume's affidavit explains that a generic drug's similar appearance to the branded product "enhances patient safety and compliance with the medically prescribed dosing regimen" and that safety and compliance "would be particularly important for ADHD drugs when non-medical intermediaries (such as school secretaries) dispense mid-day doses to children [treated for ADHD]." Blume's affidavit explains, "Dosage form similarities enhance patient acceptance" and points to generic formulations of other central nervous system drugs that are identical or mirror the brand drug in color."

Gregory Drew, a registered pharmacist and Vice President of Pharmacy Health Services for Rite Aid Corporation, explains that Rite Aid prefers that "the generic tablet look as similar to the branded tablet as possible" so as to "increase patient acceptance and comfort," as well as compliance and that "all other things being equal, Rite Aid will choose to stock the generic product that most closely resembles the branded product."⁵²

52. *Id.*

3 Labeling and Advertising

The FDA strictly controls what drug makers must, may, and may not say when marketing their drugs. (In particular, all approved drugs must have a "label" that gives detailed information on how to use them and on potential health risks from using them.) These rules depart – in several fairly significant ways – from the usual general rules for false advertising. In addition, Hatch-Waxman requires that generic versions of a drug have a label that is "the same as the labeling approved for" the drug they copy. This section explores the false-advertising and copyright issues thereby raised.

Consumer-Directed Broadcast Advertisements: Guidance for Industry
(1999) (last updated 2002)

This guidance is intended to assist sponsors who are interested in advertising their prescription human and animal drugs, including biological products for humans, directly to consumers through broadcast media, such as television, radio, or telephone communications systems.

The Federal Food, Drug, and Cosmetic Act (the Act) requires that manufacturers, packers, and distributors (sponsors) who advertise prescription human and animal drugs, including biological products for humans, disclose in advertisements certain information about the advertised product's uses and risks. For prescription drugs and biologics, the Act requires advertisements to contain "information in brief summary relating to side effects, contraindications, and effectiveness"⁵³. The resulting information disclosure is commonly called the *brief summary*.

53. 21 U.S.C. § 352(n)

The prescription drug advertising regulations⁵⁴ distinguish between print and broadcast advertisements. Print advertisements must include the brief summary, which generally contains each of the risk concepts from the product's approved package labeling. Advertisements broadcast through media such as television, radio, or telephone communications systems must disclose the product's major risks in either the audio or audio and visual parts of the presentation; this is sometimes called the *major statement*.

54. 21 CFR § 202.1

Sponsors of broadcast advertisements are also required to present a brief summary or, alternatively, may make "adequate provision ... for dissemination of the approved or permitted package labeling in connection with the broadcast presentation"⁵⁵. This is referred to as the *adequate provision* requirement. The regulations thus specify that the major statement, together with adequate provision for dissemination of the product's approved labeling, can provide the information disclosure required for broadcast advertisements.

55. 21 CFR § 202.1(e)(1)

The purpose of this guidance is to describe an approach that FDA believes can fulfill the requirement for adequate provision in connection with consumer-directed broadcast advertisements for prescription drug and biological products. The approach presumes that such advertisements:

- Are not false or misleading in any respect. For a prescription drug, this would include communicating that the advertised product is available only by prescription and that only a prescribing health-care professional can decide whether the product is appropriate for a patient.
- Present a fair balance between information about effectiveness and information about risk.
- Include a thorough major statement conveying all of the product's most important risk information in consumer-friendly language.
- Communicate all information relevant to the product's indication (including limitations to use) in consumer-friendly language.

A sponsor wishing to use consumer-directed broadcast advertise-

ments may meet the adequate provision requirement through an approach that will allow most of a potentially diverse audience to have reasonably convenient access to the advertised product's approved labeling. One acceptable approach to disseminating the product's approved labeling is described below. This approach includes the following components.

- Disclosure in the advertisement of an operating toll-free telephone number for consumers to call for the approved package labeling.
- Reference in the advertisement to a mechanism to provide package labeling to consumers with restricted access to sophisticated technology, such as the Internet, and those who are uncomfortable actively requesting additional product information or are concerned about being personally identified in their search for product information. [The FDA recommended print advertisements or "the availability of sufficient numbers of brochures containing package labeling in a variety of publicly accessible sites (e.g., pharmacies, doctors' offices, grocery stores, public libraries)."]
- Disclosure in the advertisement of an Internet web page (URL) address that provides access to the package labeling.
- Disclosure in the advertisement that pharmacists, physicians (or other healthcare providers), or veterinarians (in the case of animal drugs) may provide additional product information to consumers.

Letter from Robert Dean, Division Director, OPDP, FDA, to Eric Gervais

Aug. 7, 2015

Dear Mr. Gervais:

The Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has reviewed the Kim Kardashian Social Media Post for DICLEGIS (doxylamine succinate and pyridoxine hydrochloride) delayed-release tablets, for oral use (DICLEGIS) submitted by Duchesnay, Inc. (Duchesnay) under cover of Form FDA 2253. The social media post was also submitted as a complaint to the OPDP Bad Ad Program. The social media post is false or misleading in that it presents efficacy claims for DICLEGIS, but fails to communicate any risk information associated with its use and it omits material facts. Thus, the social media post misbrands DICLEGIS within the meaning of the FDCA and makes its distribution violative.⁵⁶ These violations are concerning from a public health perspective because they suggest that DICLEGIS is safer than has been demonstrated.

According to its FDA-approved product labeling (PI) (emphasis in original):

DICLEGIS is indicated for the treatment of nausea and vomiting of pregnancy in women who do not respond to conservative management.

Limitations of Use

DICLEGIS has not been studied in women with hyperemesis

56. 21 U.S.C. §§ 352(a), (n); 321(n); 331(a).
See 21 CFR § 202.1(e)(5)

gravidarum.

DICLEGIS is contraindicated in women with known hypersensitivity to doxylamine succinate, other ethanolamine derivative antihistamines, pyridoxine hydrochloride or any inactive ingredient in the formulation, as well as in women who are taking monoamine oxidase inhibitors (MAOIs). The PI for DICLEGIS includes Warnings and Precautions regarding activities requiring mental alertness and concomitant medical conditions. In addition, the most common adverse reaction reported with DICLEGIS was somnolence.

The social media post is misleading because it presents various efficacy claims for DICLEGIS, but fails to communicate any risk information. For example, the social media post includes the following claims:

OMG. Have you heard about this? As you guys know my #morningsickness has been pretty bad. I tried changing things about my lifestyle, like my diet, but nothing helped, so I talked to my doctor. He prescribed me #Diclegis, and I felt a lot better and most importantly, it's been studied and there was no increased risk to the baby. I'm so excited and happy with my results that I'm partnering with Duchesnay USA to raise awareness about treating morning sickness. If you have morning sickness, be safe and sure to ask your doctor about the pill with the pregnant woman on it and find out more www.diclegis.com; www.DiclegisImportantSafetyInfo.com.

The social media post, however, entirely omits **all** risk information. We note the statement, “[F]ind out more www.diclegis.com; www.DiclegisImportantSafetyInfo.com[,]” appears at the end of the social media post; however, this does not mitigate the misleading omission of risk information. By omitting the risks associated with DICLEGIS, the social media post misleadingly fails to provide material information about the consequences that may result from the use of the drug and suggests that it is safer than has been demonstrated.

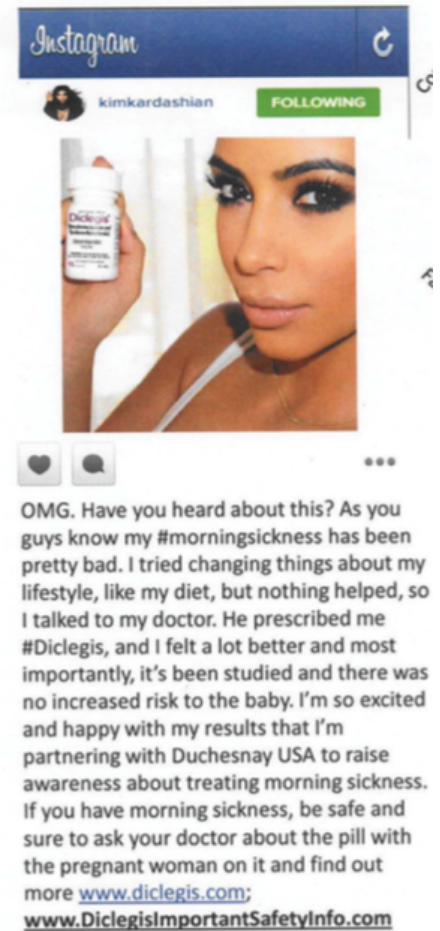
In addition, the social media post is misleading because it fails to provide material information regarding DICLEGIS’ full approved indication, including important limitations of use. Specifically, it fails to convey that DICLEGIS has not been studied in women with hyperemesis gravidarum.

OPDP requests that Duchesnay immediately cease misbranding DICLEGIS and/or cease introducing the misbranded drug into interstate commerce.

SmithKline Beecham v. Watson Pharmaceuticals

211 F.3d 21 (2d Cir. 2000)

This appeal arises out of a copyright action alleging infringement of appellant’s copyright in a user’s guide and audiotape developed for its Nicorette-brand gum. Appellees, in obtaining approval to sell a com-



The challenged Kim Kardashian Social Media Post

peting generic nicotine gum product, were directed by the FDA to use labeling almost identical to appellant's copyrighted guide and tape.

Appellees cannot be liable for copyright infringement because the Hatch-Waxman Amendments require generic drug producers to use the same labeling as was approved by the FDA for, and is used by, the producer of the pioneer drug.

Appellant SmithKline manufactures and sells Nicorette nicotine polacrilex gum, an over-the-counter product designed to help smokers overcome the cigarette habit.

Appellee Watson obtained FDA approval for the OTC marketing of a generic version of nicotine gum intended to compete directly with Nicorette. To obtain that approval from the FDA, Watson had to comply with the requirement imposed by the Hatch-Waxman Amendments that "the labeling proposed for [its] new drug [be] the same as the labeling approved for" Nicorette.⁵⁷ Thus, Watson's generic nicotine gum was accompanied by a user guide and audio tape that were virtually identical to SmithKline's.

57. 21 U.S.C. § 355(j)(2)(A)(v)

Watson asserts that this copying, having been dictated by the FDA, is a "fair use" protected under 17 U.S.C. § 107. The United States, in its *amicus curiae* brief, argues instead that in submitting its copyrighted materials for FDA approval, SmithKline gave the FDA an implied, nonexclusive license to permit or require generic drug applicants to copy the user's guide and audiotape in their own nicotine gum packaging.

In our view, the case can more easily be disposed of on the straightforward ground that the Hatch-Waxman Amendments to the FDCA not only permit but require producers of generic drugs to use the same labeling as was approved for, and is used in, the sale of the pioneer drug, even if that label has been copyrighted. Because those Amendments were designed to facilitate rather than impede the approval and OTC sale of generic drugs, the FDA's requirement that Watson use much of SmithKline's label precludes a copyright infringement action by SmithKline.

If SmithKline's copyright claim has merit, then Watson cannot realistically use the ANDA process to sell its generic nicotine gum because it will either have to change the label and lose FDA approval or be enjoined from using a label that infringes SmithKline's copyright. We are thus faced with a conflict between two statutes. The Hatch-Waxman Amendments require generic drug producers to use labeling that will infringe upon copyrights in labels of pioneer drugs. The Copyright Act seems to prohibit such copying. However, applying the familiar canon that, where two laws are in conflict, courts should adopt the interpretation that preserves the principal purposes of each, the conflict is less stark and more easily resolved than it might seem. The purposes of the Hatch-Waxman Amendments would be severely undermined if copyright concerns were to shape the FDA's application of the "same" labeling requirement.

Our point here is not only that Congress would have provided explicitly that the Hatch-Waxman Amendments trump the copyright laws

had it foreseen the statutory conflict exposed by the present action, although we firmly believe that to be obvious. Our point is also that the profit sought by the creator of the pioneer drug label flows primarily from the administrative approval of the drug and the patent and exclusivity periods free from competition that follow. The pertinent purpose of the copyright laws – to encourage the production of creative works by according authors a property right in their works so that authors will not have to share profits from their labors with free riders – is not seriously implicated by allowing the “same” labeling requirement to trump a copyright under the Hatch-Waxman Amendments. It is simply not conceivable that, if we reject SmithKline’s claim, pioneer drug producers will so fear the copying of labels by future generic drug producers that some pioneer producers – or even one of them – will lack the incentive to create labeling needed for FDA approval.