Biotechnology

12

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Biotechnology raises not one but two recurring intellectual property issues. The first is that its subject matter is a mix of the natural and the artificial. As we saw in *Mayo* and *Myriad*, drawing the line between the two can be difficult and contentious. The second distinctive problem of biotechnology is that biology is exceptionally complicated; biological systems are unpredictable and hard to model. What's more, the biological systems we most care about – living human bodies – are nost just complicated beyond our present understanding but 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 Biotech-Specific Patent Law

1 Subject Matter

This would be a good time to look back at *Mayo* and *Myriad*. This section plays out some of their implications.

In re Roslin Institute (Edinburgh)

750 F.3d 1333 (2014)

Dolly the Sheep

On July 5, 1996, Keith Henry Stockman Campbell and Ian Wilmut successfully produced the first mammal ever cloned from an adult somatic cell: Dolly the Sheep. A clone is an identical genetic copy of a cell, cell part, or organism.

Campbell and Wilmut obtained a patent on the somatic method of cloning mammals, which has been assigned to Roslin. See U.S. Patent

No. 7,514,258. The '258 patent is not before us in this appeal. Instead, the dispute here concerns the Patent and Trademark Office's (PTO) rejection of Campbell's and Wilmut's claims to the clones themselves, set forth in the '233 application, titled Quiescent Cell Populations for Nuclear Transfer.

The '233 application claims the products of Campbell's and Wilmut's cloning method: cattle, sheep, pigs, and goats. Claim 155 and 164 is representative:

> 155. A live-born clone of a pre-existing, non-embryonic, donor mammal, wherein the mammal is selected from cattle, sheep, pigs, and goats.

Chakrabarty: 447 U.S. 303 (1980)

Funk Bros.: 333 U.S. 127 (1948)

Even before the Supreme Court's recent decision in *Myriad*, the Court's opinions in *Diamond v. Chakrabarty* and *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, made clear that naturally occurring organisms are not patentable.

In *Funk Bros*, the Supreme Court considered a patent that claimed a mixture of naturally occurring strains of bacteria that helped leguminous plants extract nitrogen from the air and fix it in soil. The Court concluded that this mixture of bacteria strains was not patent eligible because the patentee did not alter the bacteria in any way. Critically, in Funk Bros., the Court explained:

> We do not have presented the question whether the methods of selecting and testing the non-inhibitive strains are patentable. We have here only product claims. The patentee does not create a state of inhibition or of non-inhibition in the bacteria. Their qualities are the work of nature. Those qualities are of course not patentable. For patents cannot issue for the discovery of the phenomena of nature. The qualities of these bacteria, like the heat of the sun, electricity, or the qualities of metals, are part of the storehouse of knowledge of all men. They are manifestations of laws of nature, free to all men and reserved exclusively to none.

Thus, while the method of selecting the strains of bacteria might have been patent eligible, the natural organism itself – the mixture of bacteria – was unpatentable because its "qualities are the work of nature" unaltered by the hand of man.

The patent at issue in *Chakrabarty* claimed a genetically engineered bacterium that was capable of breaking down various components of crude oil. The patent applicant created this non-naturally occurring bacterium by adding four plasmids to a specific strain of bacteria. The Court held that the modified bacterium was patentable because it was "new" with "markedly different characteristics from any found in nature and one having the potential for significant utility." As the Court

explained, the patentee's "discovery is not nature's handiwork, but his own."

Accordingly, discoveries that possess "markedly different characteristics from any found in nature," are eligible for patent protection. In contrast, any existing organism or newly discovered plant found in the wild is not patentable. *See also In re Beineke* (holding that a newly discovered type of plant is not eligible for plant patent protection, in part, because such a plant was not "in any way the result of the patent applicant's creative efforts or indeed anyone's creative efforts.").

Beineke: 690 F.3d 1344 (Fed. Cir. 2012)

While Roslin does not dispute that the donor sheep whose genetic material was used to create Dolly could not be patented, Roslin contends that copies (clones) are eligible for protection because they are "the product of human ingenuity" and "not nature's handiwork, but their own." Roslin argues that such copies are either compositions of matter or manufactures within the scope of § 101. However, Dolly herself is an exact genetic replica of another sheep and does not possess markedly different characteristics from any farm animals found in nature. Dolly's genetic identity to her donor parent renders her unpatentable.

Supreme Court decisions regarding the preemptive force of federal patent law confirm that individuals are free to copy any unpatentable article, such as a live farm animal, so long as they do not infringe a patented method of copying. In *Sears, Roebuck & Co. v. Stiffel Co.*, the question was whether the defendant could be held liable under state law for copying a lamp design whose patent protection had expired. The Court explained that "when the patent expires the monopoly created by it expires, too, and the right to make the article – including the right to make it in precisely the shape it carried when patented – passes to the public." The Court further clarified that "an unpatentable article, like an article on which the patent has expired, is in the public domain and may be made and sold by whoever chooses to do so." Roslin's claimed clones are exact genetic copies of patent ineligible subject matter. Accordingly, they are not eligible for patent protection.

Sears, Roebuck: 376 U.S. 225 (1964)

Roslin argues that its claimed clones are patent eligible because they are distinguishable from the donor mammals used to create them. First, Roslin contends that "environmental factors" lead to phenotypic differences that distinguish its clones from their donor mammals. A phenotype refers to all the observable characteristics of an organism, such as shape, size, color, and behavior, that result from the interaction of the organism's genotype with its environment. A mammal's phenotype can change constantly throughout the life of that organism not only due to environmental changes, but also the physiological and morphological changes associated with aging.

Roslin argues that environmental factors lead to phenotypic dif-

ferences between its clones and their donor mammals that render their claimed subject matter patentable. However, these differences are unclaimed. Indeed, the word "cloned" in the pending claims connotes genetic identity, and the claims say nothing about a phenotypic difference between the claimed subject matter and the donor mammals. Moreover, Roslin acknowledges that any phenotypic differences came about or were produced quite independently of any effort of the patentee. Contrary to Roslin's arguments, these phenotypic differences do not confer eligibility on their claimed subject matter. Any phenotypic differences between Roslin's donor mammals and its claimed clones are the result of environmental factors, uninfluenced by Roslin's efforts.

Second, Roslin urges that its clones are distinguishable from their original donor mammals because of differences in mitochondrial DNA, which originates from the donor oocyte rather than the donor nucleus. Mitochondria are the organelles (cellular bodies) that produce the energy eukaryotic cells need to function. Mitochondria possess their own DNA, which is distinct from the DNA housed in the cell's nucleus. In the cloning process, the clone inherits its mitochondrial DNA from its donor oocyte, instead of its donor somatic cell. Therefore, Dolly's mitochondrial DNA came from the oocyte used to create her, not her donor mammary cell. Roslin argues that this difference in mitochondrial DNA renders its product claims patent eligible.

But any difference in mitochondrial DNA between the donor and cloned mammals is, too, unclaimed. Furthermore, Roslin's patent application does not identify how differences in mitochondrial DNA influence or could influence the characteristics of cloned mammals.

Finally, Roslin argues that its clones are patent eligible because they are time-delayed versions of their donor mammals, and therefore different from their original mammals. But this distinction cannot confer patentability. The difficulty with the time-delayed characteristic is that it is true of any copy of an original.

Ariosa Diagnostics, Inc. v. Sequenom, Inc.

788 F. 3d 1371 (Fed. Cir. 2015)

In 1996, Drs. Dennis Lo and James Wainscoat discovered cell-free fetal DNA ("cffDNA") in maternal plasma and serum, the portion of maternal blood samples that other researchers had previously discarded as medical waste. cffDNA is non-cellular fetal DNA that circulates freely in the blood stream of a pregnant woman. Applying a combination of known laboratory techniques to their discovery, Drs. Lo and Wainscoat implemented a method for detecting the small fraction of paternally inherited cffDNA in maternal plasma or serum to determine fetal characteristics, such as gender. The invention, commercialized by Sequenom as its MaterniT21 test, created an alter-

native for prenatal diagnosis of fetal DNA that avoids the risks of widely-used techniques that took samples from the fetus or placenta. In 2001, Drs. Lo and Wainscoat obtained U.S Patent No. 6,258,540, which relates to this discovery.

The parties agree that the patent does not claim cffDNA or paternally inherited cffDNA. Instead, the '540 patent claims certain methods of using cffDNA. The steps of the method of claim 1 of the '540 patent include amplifying the cffDNA contained in a sample of a plasma or serum from a pregnant female and detecting the paternally inherited cffDNA. Amplifying cffDNA results in a single copy, or a few copies, generating thousands to millions of copies of that particular DNA sequence. In the amplification step, DNA is extracted from the serum or plasma samples and amplified by polymerase chain reaction ("PCR") or another method. PCR exponentially amplifies the cffDNA sample to detectable levels.

Ariosa makes and sells the Harmony Test, a non-invasive test used for prenatal diagnosis of certain fetal characteristics. [Sequenom threatened suit and Ariosa filed an action seeking a declaratory judgment of noninfringement.]

It is undisputed that the existence of cffDNA in maternal blood is a natural phenomenon. Sequenom does not contend that Drs. Lo and Wainscoat created or altered any of the genetic information encoded in the cffDNA, and it is undisputed that the location of the nucleic acids existed in nature before Drs. Lo and Wainscoat found them. The method ends with paternally inherited cffDNA, which is also a natural phenomenon. The method therefore begins and ends with a natural phenomenon. Thus, the claims are directed to matter that is naturally occurring.

Because the claims at issue are directed to naturally occurring phenomena, we turn to the second step of *Mayo*'s framework. In the second step, we examine the elements of the claim to determine whether the claim contains an inventive concept sufficient to "transform" the claimed naturally occurring phenomenon into a patenteligible application. For process claims that encompass natural phenomenon, the process steps are the additional features that must be new and useful.

Like the patentee in *Mayo*, Sequenom contends that the claimed methods are patent eligible applications of a natural phenomenon, specifically a method for detecting paternally inherited cffDNA. Using methods like PCR to amplify and detect cffDNA was well-understood, routine, and conventional activity in 1997. The method at issue here amounts to a general instruction to doctors to apply routine, conventional techniques when seeking to detect cffDNA. Because the method steps were well-understood, conventional and routine, the method of detecting paternally inherited cffDNA is not new and useful. The only subject matter new and useful as of the date of

the application was the discovery of the presence of cffDNA in maternal plasma or serum.

Sequenom argues that there are numerous other uses of cffDNA aside from those claimed in the '540 patent, and thus, the '540 patent does not preempt all uses of cffDNA. While preemption may signal patent ineligible subject matter, the absence of complete preemption does not demonstrate patent eligibility. In this case, Sequenom's attempt to limit the breadth of the claims by showing alternative uses of cffDNA outside of the scope of the claims does not change the conclusion that the claims are directed to patent ineligible subject matter. Where a patent's claims are deemed only to disclose patent ineligible subject matter under the *Mayo* framework, as they are in this case, preemption concerns are fully addressed and made moot.

Linn, Circuit Judge, concurring:

I join the court's opinion invalidating the claims of the '540 patent only because I am bound by the sweeping language of the test set out in *Mayo*. In my view, the breadth of the second part of the test was unnecessary to the decision. This case represents the consequence – perhaps unintended – of that broad language in excluding a meritorious invention from the patent protection it deserves and should have been entitled to retain.

The Supreme Court's blanket dismissal of conventional post-solution steps leaves no room to distinguish *Mayo* from this case, even though here no one was amplifying and detecting paternally-inherited cffDNA using the plasma or serum of pregnant mothers. Indeed, the maternal plasma used to be routinely discarded, because, as Dr. Evans testified, "nobody thought that fetal cell-free DNA would be present."

It is hard to deny that Sequenom's invention is truly meritorious. Prior to the '540 patent, prenatal diagnoses required invasive methods, which presented a degree of risk to the mother and to the pregnancy. The available techniques were time-consuming or required expensive equipment. In a groundbreaking invention, Drs. Lo and Wainscoat discovered that there was cell-free fetal DNA in the maternal plasma. The Royal Society lauded this discovery as "a paradigm shift in non-invasive prenatal diagnosis," and the inventors' article describing this invention has been cited well over a thousand times. The commercial embodiment of the invention, the MaterniT21 test, was the first marketed non-invasive prenatal diagnostic test for fetal aneuploidies, such as Down's syndrome, and presented fewer risks and a more dependable rate of abnormality detection than other tests. Unlike in *Mayo*, the '540 patent claims a new method that should be patent eligible. While the instructions in the claims at issue in *Mayo* had been widely used by doctors – they had been measuring metabo-

lites and recalculating dosages based on toxicity/inefficacy limits for years – here, the amplification and detection of cffDNA had never before been done. The new use of the previously discarded maternal plasma to achieve such an advantageous result is deserving of patent protection.

In short, Sequenom's invention is nothing like the invention at issue in *Mayo*. But for the sweeping language in the Supreme Court's *Mayo* opinion, I see no reason, in policy or statute, why this breakthrough invention should be deemed patent ineligible.

DNA Copyright Problem

Two law professors collaborated with a biotechnology company to create what they called "Prancer":

> a DNA sequence that provides a set of instructions for the synthesis of a protein comprising 231 amino acids linked together in a specific order. The set of instructions is coded in the standard genetic code, and is interpretable by most living biological systems. The encoded protein is fluorescent, which is a useful functional attribute in biotechnology.

The Copyright Office said "no." Its reasoning, along with the professors' response, are detailed in Christopher M. Holman, Claes Gustafsson, & Andrew W. Torrance, *Are Engineered Genetic Sequences Copyrightable?*, 35 Biotech. L. Rep. 103 (2016). But try not to peek before you try your hand at coming up with the best reasons for and against!

Is Prancer a copyrightable work of authorship?

2 Ownership

The doctrines here are familiar. *Schering* illustrates some of the inherent difficulty in determining novelty (and also infringement) given that biological systems transform substances in complex ways. *Eli Lilly v. Zenith* considers the novelty implications of clinical drug testing.

Schering Corp. v. Geneva Pharmaceuticals

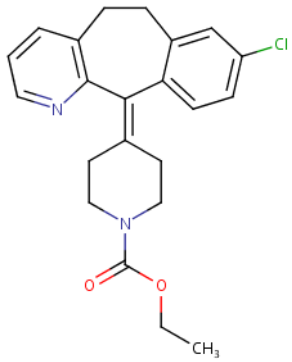
339 F.3d 1373 (Fed. Cir. 2003)

The District Court correctly determined that that U.S. Patent No. 4,282,233 inherently anticipates claims 1 and 3 of Patent No. 4,659,716.

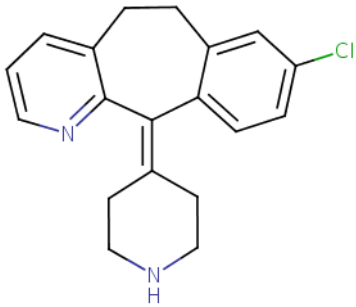
Schering owns the '233 and '716 patents on antihistamines. Antihistamines inhibit the histamines that cause allergic symptoms.

The prior art '233 patent covers the antihistamine loratadine, the active component of a pharmaceutical that Schering markets as CLARITIN. Unlike conventional antihistamines when CLARITIN was launched, loratadine does not cause drowsiness.

The more recent '716 patent at issue in this case covers a metabolite of loratadine called descarboethoxyloratadine (DCL).. A metabolite is the compound formed in the patient's body upon ingestion of a pharmaceutical. The ingested pharmaceutical undergoes a chemical



Loratadine



Descarboethoxyloratadine

conversion in the digestion process to form a new metabolite compound. The metabolite DCL is also a non-drowsy antihistamine. The '716 patent issued in April 1987 and will expire in April 2004 (the '233 patent issued in 1981 and has since expired).

A patent is invalid for anticipation if a single prior art reference discloses each and every limitation of the claimed invention. Moreover, a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference. Inherent anticipation does not require that a person of ordinary skill in the art at the time would have recognized the inherent disclosure.

DCL is not formed accidentally or under unusual conditions when loratadine is ingested. The record shows that DCL necessarily and inevitably forms from loratadine under normal conditions. DCL is a necessary consequence of administering loratadine to patients.

This court recognizes that this may be a case of first impression, because the prior art does not disclose any compound that is identifiable as DCL. In this court's prior inherency cases, a single prior art reference generally contained an incomplete description of the anticipatory subject matter, i.e., a partial description missing certain aspects. Inherency supplied the missing aspect of the description.

This court sees no reason to modify the general rule for inherent anticipation in a case where inherency supplies the entire anticipatory subject matter. The patent law principle "that which would literally infringe if later in time anticipates if earlier," bolsters this conclusion. Similarly, if granting patent protection on the disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated. The public remains free to make, use, or sell prior art compositions or processes, regardless of whether or not they understand their complete makeup or the underlying scientific principles which allow them to operate. The doctrine of anticipation by inherency, among other doctrines, enforces that basic principle. Thus, inherency operates to anticipate entire inventions as well as single limitations within an invention.

Turning to this case, the use of loratadine would infringe claims 1 and 3 of the '716 patent covering the metabolite DCL. This court has recognized that a person may infringe a claim to a metabolite if the person ingests a compound that metabolizes to form the metabolite. An identical metabolite must then anticipate if earlier in time than the claimed compound.

This court's conclusion on inherent anticipation in this case does not preclude patent protection for metabolites of known drugs. With proper claiming, patent protection is available for metabolites of known drugs. *Cf. In re Kratz* (stating that a naturally occurring strawberry constituent compound does not anticipate claims to the sub-

Kratz: 592 F.2d 1169 (CCPA 1979)

stantially pure compound); *In re Bergstrom* (stating that a material occurring in nature in less pure form does not anticipate claims to the pure material).

Bergstrom: 427 F.2d 1394 (CCPA 1970)

But those metabolites may not receive protection via compound claims. In this case, for instance, claims 1 and 3 broadly encompass compounds defined by structure only. Such bare compound claims include within their scope the recited compounds as chemical species in any surroundings, including within the human body as metabolites of a drug. As this case holds, these broad compound claims are inherently anticipated by a prior art disclosure of a drug that metabolizes into the claimed compound.

A skilled patent drafter, however, might fashion a claim to cover the metabolite in a way that avoids anticipation. For example, the metabolite may be claimed in its pure and isolated form, as in *Kratz* and *Bergstrom*, or as a pharmaceutical composition (e.g., with a pharmaceutically acceptable carrier). The patent drafter could also claim a method of administering the metabolite or the corresponding pharmaceutical composition. The '233 patent would not provide an enabling disclosure to anticipate such claims because, for instance, the '233 patent does not disclose isolation of DCL.

Eli Lilly and Co. v. Zenith Goldline Pharm. Inc.

364 F. Supp. 2d 820 (S.D. Ind. 2005)

Olanzapine is an antipsychotic approved for the treatment of schizophrenia and bipolar disorder; Eli Lilly marketed it under the brand name ZPYREXA.

Defendants have failed to prove by clear and convincing evidence that the HGAA, HGAB, and HGAC Phase I clinical trials of olanzapine were public. These studies were conducted by Lilly personnel in the Lilly clinic. Lilly restricted access to the facility and provided full-time security. In addition, the studies were fully controlled by Lilly. The volunteers, who were healthy and not suffering from schizophrenia, were paid by Lilly for their services, remained in the research ward for the duration of the study, and were closely monitored by doctors and medical staff employed by Lilly. Only Lilly employees administered the drug. The fact that the volunteers were allowed visitors does not change the analysis.

Defendants' argument that the clinical trials were "public" because the patients did not sign a confidentiality agreement is unpersuasive and legally unsound. First, because the patients were not informed of the identity of the compound they were taking and were kept at Lilly facilities at all times, a confidentiality agreement would have been superfluous. Second, the presence or absence of a confidentiality agreement is not controlling. It is simply one of many factors to be taken into consideration.

Even if Lilly's Phase I clinical trials of olanzapine constituted a public use of the compound more than one year prior to Lilly's application for its patent, it was an experimental use. The evidence demonstrates that the art with respect to this type of atypical antipsy-

chotic drug was highly unpredictable. Small structural changes led to very different properties. Furthermore, the art was plagued with unpredicted side effects that rendered otherwise promising compounds useless in the clinical setting. These side effects could only be understood when the compounds were tested in actual patients. Olanzapine was conceived as a compound that would have antipsychotic activity but not produce flumezapine's toxic effects in schizophrenic patients. Accordingly, testing olanzapine in actual schizophrenic patients was required to prove it would "work for its intended purpose," i.e., as a safe, atypical antipsychotic drug used to treat human patients suffering from or susceptible to psychotic disorders. These Phase I clinical trials in healthy human volunteers were required by regulatory agencies before the compound could be tested in schizophrenic patients. For these reasons, the clinical tests constitute an experimental use and negate a finding that they were a "public use" as defined in patent law.

3 Infringement: Similarity

When are two substances the "same" for purposes of patent infringement? In the biotechnology context, the answer is not always straightforward.

Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.

320 F.3d 1339 (Fed. Cir. 2003)

Porcine Reproductive Respiratory Syndrome (also known as "Mystery Swine Disease" or Swine Infertility and Respiratory Syndrome), swept through commercial pig herds in the 1980s. A previously unknown disease, PRRS had its most pronounced effect on young and newborn piglets. Up to thirty percent of the piglets in litters from infected sows were stillborn, and up to eighty percent of piglets in infected herds died before weaning. The financial consequences to the commercial pig industry were severe.

Researchers seeking a cause for PRRS could not identify any known pathogen behind the epidemic (hence the name "Mystery Swine Disease"). Scientists at Boehringer were the first to solve the mystery, discovering that a previously unknown virus was responsible for the disease.

Boehringer began with a homogenate of lung, brain, spleen, liver, and kidney tissues from an infected piglet. Samples of this combined homogenate were then added to a panel of 15 different cultured mammalian cell lines. While viruses themselves are too small to see without the aid of an electron microscope, a viral infection often gives rise to morphological changes in the host cell. An observable change in a host cell due to viral infection is known as a cytopathic effect, or CPE. These changes may include cell rounding, disorientation, swelling or

shrinking, death, or detachment from the culture surface, and are visible with ordinary microscopes as perturbations of the cultured cell monolayer. Boehringer's scientists found evidence of a virus present in PRRS-infected animals when they observed a CPE in cultured MA–104 embryonic monkey kidney cells, one of the 15 cell lines inoculated with PRRS homogenate.

Continued propagation of a virus requires that the virus be passaged, which entails removing [a portion] of the culture and adding it to a fresh culture of cells. Boehringer scientists passaged the PRRS virus eight times on MA–104 cells, and deposited a sample of the virus from the eighth passage with the American Type Culture Collection (ATCC), which assigned it deposit number VR–2332.

The '778 patent claims this process for growing and isolating the PRRS virus: inoculating cultured monkey cells with the PRRS virus, and incubating the inoculated cells until a CPE is observed. Claim 2 is the only claim at issue in this case, and depends from claim 1:

1. A method of growing and isolating swine infertility and respiratory syndrome virus, ATCC–VR2332, which comprises inoculating the virus on a full or partial sheet of simian cells in the presence of serum in a suitable grown medium and incubating the inoculated cell sheet at about 34 C. to 37 C. until CPE is observed.
2. The method as recited in claim 1 wherein the simian cell line is MA–104.

Schering, like Boehringer, developed a vaccine against PRRS by attenuating the PRRS virus in cell culture. Attenuation is a process wherein a virus is repeatedly passaged on a cultured cell line, sometimes under altered culture conditions (such as lowered temperature). Variant viruses that are better adapted to grow on the cultured cell line will grow faster than the original virus; after many serial passages, such a variant will completely replace the original in the culture. Frequently, however, those variants adapted to grow in a particular environment (such as cultured monkey kidney cells) are ill-suited to grow or cause disease in the original environment (a live pig). If the attenuated virus will not productively infect pigs, but retains enough structural similarity to the original virus such that an immune response mounted against the attenuated virus will protect the pig against the original virus, then the attenuated virus may be used as a vaccine to protect against PRRS. Both Boehringer and Schering developed attenuated viruses effective as vaccines against PRRS.

Boehringer filed suit against Schering, alleging that Schering's vaccine virus, which is also grown on MA–104 monkey kidney cells, was prepared by a process that infringed the method claimed by the '778 patent.

Boehringer argues that the term "ATCC–VR2332" should be understood as a "prototype" or "generic" term for all PRRS viruses, rather than as a reference to the deposited strain. Boehringer chose to claim its virus using the term "ATCC–VR2332," a term on its face referring to a particular ATCC deposit. Boehringer did not use the broader term "PRRS virus," nor did Boehringer attempt to claim the virus in terms of the more general functional and structural properties disclosed by the specification. Boehringer did not choose to define the term "ATCC–VR2332" in the specification, nor did Boehringer state that ATCC–VR2332 was a "generic" or "prototype" virus, nor did Boehringer assert that viruses related to but not identical to the isolated strain were within the scope of the invention. These choices must be held against it. We therefore conclude that the district court properly construed "ATCC–VR2332" to refer to the strain of virus deposited with the ATCC.

Schering argues that no reasonable jury could find that Schering's VR2525 virus is equivalent to the ATCC–VR2332 viral strain recited by the claim in suit. Under the "function-way-result" analysis, Schering focuses on the fact that ATCC–VR2332 is a pathogenic virus, causing PRRS, while Schering's VR2525 is not. Schering argues that this distinction precludes a finding of equivalence, because Schering's virus generates a protective immune response when administered to pigs, while a pig inoculated with ATCC–VR2332 develops PRRS. Thus, when administered to pigs, VR2525 resembles ATCC–VR2332 in neither function, way, nor result. Schering's argument, however, flies in the face of the basic principle that the relevant analysis is of the role played by each element in the context of the specific patent claim, not whether the accused element is capable of performing different roles than the claim element in other contexts. What happens when the virus is administered to a pig is irrelevant to the assessment of whether the two viral strains are equivalent in the in vitro culture method defined by claim 2. The jury was presented with expert testimony from which it could conclude that VR2525 plays the same role as VR2332 in performance of the claimed method. The fact that, in other contexts, VR2525 can perform other functions in different ways to yield a different result is not relevant.

Schering further argues that a finding of no substantial differences is precluded by the evidence that there are at least 73 nucleotide differences between VR2525 and ATCC–VR2332 in a particular region of their RNA genomes. Schering's expert (as well as Boehringer's) noted that even a single nucleotide substitution can have a substantial effect on viral function. Schering proposes that in the face of this evidence, no reasonable jury could have concluded that two viruses having at least 73 nucleotide divergences lack substantial differences.

However, the uncontroversial fact that even a single nucleotide or

amino acid substitution may drastically alter the function of a gene or protein is not evidence of anything at all. The mere possibility that a single mutation could affect biological function cannot as a matter of law preclude an assertion of equivalence, and Schering made no showing that any of these substitutions actually affected any property of the virus relevant to the claim at hand. While it may be reasonable to assume that genetic similarity is a relevant comparison between the viruses for purposes of the claimed method, the jury was presented with expert testimony that the two viral genomes are highly similar overall and that any differences between the two are insignificant. A reasonable jury could easily rely on this testimony to conclude that the genetic differences between VR2525 and ATCC–VR2332 are insubstantial in the context of the claimed method.

B Drug Approval

The Food and Drug Administration oversees one of the most intensive regulatory regimes in the whole of the U.S. Code. 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? 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. (*Medtronic* 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.

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)

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.

1 Patent Issues

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.

Kara B. Swanson
Food and Drug Law as Intellectual Property Law

2011 Wisc. L. Rev. 331

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 *United States v. Johnson*. 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.

Johnson: 221 U.S. 488 (1911)

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 distributer. 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 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)

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

The Federal Food, Drug, and Cosmetic Act (FDCA) 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." 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." 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.

21 U. S. C. § 355(i)(1)(A);

21 U.S.C. § 355(b)(1)

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 seventeen years, . . . the right to exclude others from making, using, or selling the invention throughout the United States." 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.". 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.

Now twenty years.

35 U.S.C. § 154.

35 U.S.C. § 271(a)

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 infor-

Roche v. Bolar: 733 F. 2d 858 (Fed. Cir. 1984)

mation necessary to apply for regulatory approval. *See Roche Products, Inc. v. Bolar Pharmaceutical Co.* 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.

Informally known as Hatch-Waxman, after its Congressional champions

The Drug Price Competition and Patent Term Restoration Act of 1984 sought to eliminate this distortion from both ends of the patent 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:

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

(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) …

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."

35 U.S.C. § 271(e)(1)

The distortion at the other end of the patent period was addressed by § 202 of the Act. That added to the provision prohibiting patent infringement, 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 core of the present controversy is that petitioner interprets the statutory phrase, "a Federal law which regulates the manufacture, use, or sale of drugs," to refer only to those individual provisions of federal law that regulate drugs, whereas respondent interprets it to refer to the entirety of any Act (including, of course, the FDCA) at least some of whose provisions regulate drugs. If petitioner is correct, only such provisions of the FDCA as § 505, governing premarket approval of new drugs, are covered by § 271(e)(1), and respondent's submission of information under FDCA § 515, governing premarket approval of medical devices, would not be a noninfringing use.

It seems most implausible to us that Congress, being demonstrably aware of the *dual* distorting effects of regulatory approval requirements in this entire area – dual distorting effects that were roughly offsetting, the disadvantage at the beginning of the term producing a more or less corresponding advantage at the end of the term – should choose to address both those distortions only for drug products; and for other products named in § 201 should enact provisions which not only leave in place an anticompetitive restriction at the end of the monopoly term but simultaneously expand the monopoly term itself, thereby not only failing to eliminate but positively aggravating distortion of the 17-year patent protection. It would take strong evidence to persuade us that this is what Congress wrought, and there is no such evidence here.

Merck v. Integra 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."

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 course of clinical testing and regulatory filing. So some firms tried to argue that generic drugs required no new approval from the FDA (*Generix*).

In 1984, Congress enacted a grand bargain between pioneer and generic firms commonly known as Hatch-Waxman 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 (*Actavis*).
2. It then prohibits the FDA from approving ANDAs during certain statutory exclusivity periods. *Actavis Elizabeth* illustrates, and Erika Lietzan discusses.

3. It creates specialized procedures to sort out conflicting claims over patents potentially reading on generic drugs (*Caraco*).
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. *FTC v. Actavis* illustrates the economic significance of this exclusivity.

United States v. Generix Drug Corp.

460 U.S. 453 (1983)

The active ingredients in most prescription drugs constitute less than 10% of the product; inactive "excipients" (such as coatings, binders, and capsules) constitute the rest. The term "generic drug" is used to describe a product that contains the same active ingredients but not necessarily the same excipients as a so-called "pioneer drug" that is marketed under a brand name.[1] Respondent Generix is a distributor of generic drugs manufactured by other firms.

The Government initiated this action to enjoin Generix from distributing in interstate commerce a number of generic drug products that contain eight specified active ingredients. It alleged that the FDA had never approved new drug applications with respect to any of those products.

The Court of Appeals for the Fifth Circuit, now the Eleventh Circuit held that the statutory prohibition against the sale of a "new drug" without prior approval does not apply to a drug product having the same active ingredients as a previously approved drug product, regardless of any differences in excipients. It based that conclusion on its view that the statutory requirement of evaluating the safety and effectiveness of new drugs must normally relate to active ingredients, because the precise technique of formulating the finished drug is not part of the information generally known to the medical or scientific community. Moreover, it believed that the legislative history suggested that Congress had not intended to create a product-by-product licensing system.

The Court of Appeals misread the statutory text. Generic drug products are quite plainly drugs within the meaning of the FDCA.

FTC v. Actavis, Inc.

133 S. Ct. 2223 (2013)

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 test-

[1] Generic drugs, also called "copycat" or "me-too" drugs, are usually marketed at relatively low prices because their manufacturers do not incur the research, development, and promotional costs normally associated with the creation and marketing of an original product.

ing 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 piggy-back on the pioneer's approval efforts, speeds the introduction of low-cost generic drugs to market, thereby furthering drug competition.

Actavis Elizabeth LLC v. U.S. Food and Drug Admin.

625 F.3d 760 (D.C. Cir. 2010)

The Hatch–Waxman Amendments allowed generic versions of previously approved drugs to gain approval through the submission of an ANDA. These abbreviated applications reduce the effort required to gain marketing approval by, among other things, allowing the applicant to rely on clinical studies submitted as part of a previous new drug application.

The Hatch–Waxman Amendments also grant various periods of marketing exclusivity to certain pioneer drugs. 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 …

21 U.S.C § 355(j)(5)(f)(ii)

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 "contains. reports of new clinical investigations … essential to the approval of the application and con-

21 U.S.C. § 355(j)(5)(F)(iii)

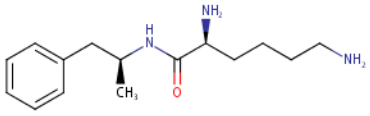
The Best Pharmaceuticals for Children Act gives six moths of additional exclusivity if the applicant conducts certain require forms of pediatric testing. *See* 21 U.S.C. § 355a.

21 C.F.R. § 314.108(a) & (b)(2))

ducted or sponsored by the applicant."

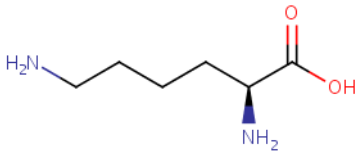
The FDA has implemented these exclusivity provisions through regulations. The regulations give five years of exclusivity for each "drug product that contains a new chemical entity.". A "new chemical entity" is "a drug that contains no active moiety that has been approved by FDA in any other" new drug application. "Active moiety" is defined as "the molecule or ion … responsible for the physiological or pharmacological action of the drug substance." [Various related forms of molecules or ions, including esters, salts, and other forms that differ only in their noncovalent bonds, are considered to be the same "active moiety."]

In 2007, the Food and Drug Administration approved Vyvanse, a name-brand drug for the treatment of attention deficit hyperactivity disorder. Two years later, Actavis submitted an application for lisdexamfetamine dimesylate, a generic version of the same drug. The FDA returned Actavis' application. It did so because it had previously determined that Vyvanse was entitled to five years of marketing exclusivity under the Hatch-Waxman Amendments to the Federal Food, Drug, and Cosmetic Act. Actavis brought this action claiming that Vyvanse was not entitled to five years of exclusivity.



Lisdexamfetamine

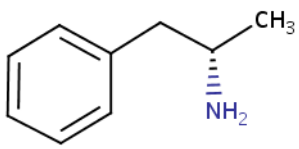
Lisdexamfetamine dimesylate is a salt of lisdexamfetamine. Since, under the agency's regulations, salts are not considered active moieties, the agency's analysis centered on the lisdexamfetamine molecule alone. Lisdexamfetamine consists of a portion of lysine, a common amino acid, connected to dextroamphetamine. These two parts are linked by [a covalent bond]. Once it enters the body, lisdexamfetamine undergoes a chemical conversion to produce dextroamphetamine.



Lysine

Actavis thinks this language [quoted above] prevents the FDA from granting five-year exclusivity to any drug containing a drug molecule (such as lisdexamfetamine) that eventually produces a previously approved drug molecule in the body.

Actavis relies mainly on the term "active ingredient," which it says obligates the FDA to identify the particular drug molecule that reaches the "site" of the drug's action. This molecule, Actavis argues, is necessarily the "active ingredient" of the drug in question, regardless of the form of the molecule before it enters the body. But there is nothing to indicate that Congress used the term in the sense Actavis urges. The Hatch–Waxman Amendments do not define active ingredient. The legislative history establishes only that Congress was concerned with providing incentives for innovation by granting five-year exclusivity to "new chemical entities" and is silent on what determines novelty.



Dextroamphetamine

Actavis argues that by using the term "active," Congress was requiring the FDA to determine the particular molecule that provides

the drug's "activity," which it claims is limited to the drug's specific therapeutic effect. If this molecule has been previously approved, then five-year exclusivity is not warranted. But the FDA is right—or at least we have been given no reason to doubt – that the activity of a drug cannot be reduced to such a simple formulation. The agency has concluded that the entire pre-ingestion drug molecule should be deemed responsible for the drug's activity, which can include its "distribution within the body, its metabolism, its excretion, or its toxicity." There is no reason to believe Congress thought differently – or thought about it at all.

In the FDA's view, drug derivatives such as lisdexamfetamine *are* "major innovations" deserving five-year exclusivity. The FDA's regulations leave many types of drug derivatives eligible only for three-year exclusivity. The FDA's policy is based on its view that drug derivatives containing covalent bonds are, on the whole, distinct from other types of derivative drugs such that the former are uniquely deserving of "new chemical entity" status and the resulting five-year exclusivity. We are hard pressed to second-guess the FDA's view, especially since it rests on the agency's evaluations of scientific data within its area of expertise. At best, Actavis has offered evidence that some covalent structural changes do not alter the basic properties of the drug in question and that some noncovalent structural changes do. But agencies may employ bright-line rules for reasons of administrative convenience, so long as those rules fall within a zone of reasonableness and are reasonably explained. The FDA has explained that its policy is based in part on the "difficulty in determining precisely which molecule, or portion of a molecule, is responsible for a drug's effects." Nothing in the record establishes that the FDA's approach is unreasonable. Given the complexity of the statutory regime, we defer to the agency's interpretation.

Note that Hatch-Waxman NCE active-ingredient exclusivity applies only to ANDAs. Actavis remained free to submit a full NDA in support of its proposal to market lisdexamfetamine dimesylate.

Erika Lietzan

The Myths of Data Exclusivity

20 Lewis & Clark L. Rev. 91 (2016)

Lietzan defines data exclusivity as "prohibitions on submission or approval of *abbreviated* applications, which implicitly or explicitly rely on previously submitted data."

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 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 gov-

ernment 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.

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?

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. 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- terizing 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.

Lietzan defines market exclusivity as "prohibitions on submission or approval of any competing application, even if supported by a full complement of original data."

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 dis- ease affects fewer than 200,000 persons in this country or that the com- pany 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.

Caraco Pharmaceutical Labs v. Novo Nordisk

132 S. Ct. 1670 (2012)

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 compound 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 number 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

21 U.S.C. S S 355(b)(1)

more officially denominated Approved Drug Products with Therapeutic Equivalence Evaluations).

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 authored 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.". 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.. Assuming the brand does so, the FDA generally

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

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

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, *Mylan Pharmaceuticals, Inc. v. Thompson*, 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.

Mylan v. THompson: 268 F.3d 1323 (Fed. Cir. 2001)

Congress responded to these abuses by creating a mechanism, 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 counterclaim 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."

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

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.

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 market-

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."

ing 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.

Consider the point as applied to this case. Caraco wishes to market a generic version of repaglinide for two (and only two) uses. Under the statute, the FDA could approve Caraco's application so long as no patent covers those uses, regardless whether a patent protects yet a third method of using the drug. Novo agrees that Caraco could bring a counterclaim if Novo's assertion of patent protection for repaglinide lacked any basis – for example, if Novo held no patent, yet claimed rights to the pair of uses for which Caraco seeks to market its drug. But because Novo has a valid patent on a *different* use, Novo argues that Caraco's counterclaim evaporates. And that is so even though, once again, Caraco has no wish to market its product for that patented use and the FDA stands ready, pursuant to the statute, to approve Caraco's product for the other two. To put the matter simply, Novo thinks the counterclaim disappears because it has a patent for a method of use in which neither Caraco nor the FDA is interested at all.

Another aspect of the counterclaim provision – its description of available remedies–dispatches whatever remains of Novo's arguments. According to the statute, a successful claimant may obtain an order requiring the brand to "correct or delete" its patent information. Our interpretation of the statute gives content to both those remedies: It deletes a listing from the Orange Book when the brand holds no relevant patent and corrects the listing when the brand has misdescribed the patent's scope. By contrast, Novo's two arguments would all but read the term "correct" out of the statute.

FTC v. Actavis, Inc.

133 S.Ct. 2223 (2013)

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. And the basic question here is whether such an agreement can sometimes unreasonably diminish competition in violation of the an-

titrust laws.

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.

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.. It can certify that the brand-name manufacturer has not listed any relevant patents. It can certify that 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, 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.

21 U.S.C. § 355(j)(2)(A)(vii)

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). 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.

21 U.S.C § 355(j)(5)(B)(iv)

In 1999, Solvay Pharmaceuticals, a respondent here, filed a New Drug Application for a brand-name drug called AndroGel. The FDA approved the application in 2000. In 2003, Solvay obtained a relevant patent and disclosed that fact to the FDA, as Hatch-Waxman requires.

Later the same year another respondent, Actavis, Inc. (then known as Watson Pharmaceuticals), filed an Abbreviated New Drug

Application for a generic drug modeled after AndroGel. [Other parties omitted.] Solvay initiated paragraph IV patent litigation against Actavis and Paddock. Thirty months later the FDA approved Actavis' first-to-file generic product, but, in 2006, the patent-litigation parties all settled. Under the terms of the settlement Actavis agreed that it would not bring its generic to market until August 31, 2015, 65 months before Solvay's patent expired (unless someone else marketed a generic sooner). Actavis also agreed to promote AndroGel to urologists. Solvay agreed to pay an estimated $19-$30 million annually, for nine years, to Actavis. The companies described these payments as compensation for other services Actavis promised to perform, but the FTC contends the other services had little value. According to the FTC the true point of the payments was to compensate Actavis for agreeing not to compete against AndroGel until 2015.

On January 29, 2009, the FTC filed this lawsuit against all the settling parties. The FTC's complaint alleged that respondents violated § 5 of the Federal Trade Commission Act by unlawfully agreeing "to share in Solvay's monopoly profits, abandon their patent challenges, and refrain from launching their low-cost generic products to compete with AndroGel for nine years."

15 U.S.C. § 45

Solvay's patent, if valid and infringed, might have permitted it to charge drug prices sufficient to recoup the reverse settlement payments it agreed to make to its potential generic competitors. And we are willing to take this fact as evidence that the agreement's anticompetitive effects fall within the scope of the exclusionary potential of the patent. But we do not agree that that fact, or characterization, can immunize the agreement from antitrust attack.

This Court's precedents make clear that patent-related settlement agreements can sometimes violate the antitrust laws. For one thing, to refer simply to what the holder of a valid patent could do does not by itself answer the antitrust question. The patent here may or may not be valid, and may or may not be infringed. And that exclusion may permit the patent owner to charge a higher-than-competitive price for the patented product. But an *invalidated* patent carries with it no such right. And even a valid patent confers no right to exclude products or processes that do not actually infringe. The paragraph IV litigation in this case put the patent's validity at issue, as well as its actual preclusive scope. The parties' settlement ended that litigation. The FTC alleges that in substance, the plaintiff agreed to pay the defendants many millions of dollars to stay out of its market, even though the defendants did not have any claim that the plaintiff was liable to them for damages. That form of settlement is unusual. There is reason for concern that settlements taking this form tend to have significant adverse effects on competition.

Given these factors, it would be incongruous to determine an-

titrust legality by measuring the settlement's anticompetitive effects solely against patent law policy, rather than by measuring them against procompetitive antitrust policies as well. Rather, the general procompetitive thrust of the Hatch-Waxman Act, its specific provisions facilitating challenges to a patent's validity, and its later-added provisions requiring parties to a patent dispute triggered by a paragraph IV filing to report settlement terms to the FTC and the Antitrust Division of the Department of Justice, all suggest the contrary.

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.

The FTC urges us to hold that reverse payment settlement agreements are presumptively unlawful and that courts reviewing such agreements should proceed via a "quick look" approach, rather than applying a "rule of reason." We decline to do so. That is because the likelihood of a reverse payment bringing about anticompetitive

effects depends upon its size, its scale in relation to the payor's anticipated future litigation costs, its independence from other services for which it might represent payment, and the lack of any other convincing justification. The existence and degree of any anticompetitive consequence may also vary as among industries. These complexities lead us to conclude that the FTC must prove its case as in other rule-of-reason cases.

To say this is not to insist that the Commission need litigate the patent's validity, empirically demonstrate the virtues or vices of the patent system, present every possible supporting fact or refute every possible pro-defense theory. We leave to the lower courts the structuring of the present rule-of-reason antitrust litigation.

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.

Genentech, Inc. v. Bowen

676 F. Supp. 301 (D.D.C. 1987)

As food and drug regulatory statues 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," 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."

21 U.S.C. § 360bb

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 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 application … 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. …

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.

Sigma-Tau Pharmaceuticals, Inc. v. Schwetz

288 F.3d 141 (4th Cir. 2002)

Sigma-Tau Pharmaceuticals developed a drug to treat a rare condition known as carnitine deficiency in people with inborn metabolic disorders.[1] The FDA designated Sigma-Tau's levocarnitine drug an "orphan drug" and approved Sigma-Tau's application to market it. Its exclusivity for inborn metabolic disorders expired in 1999.

Sigma-Tau later received FDA approval for use of its levocarnitine drug for the prevention and treatment of a second rare condition – carnitine deficiency in patients with end-stage renal disease who are undergoing dialysis. Sigma-Tau's exclusivity for treating carnitine

[1] Carnitine deficiency can manifest itself in many ways, including the failure to thrive in infants, cardiomyopathy, recurrent infections, muscle weakness, and liver dysfunction.

deficiency in ESRD patients expires in 2006.

The FDA recently approved the applications of two drug manufacturers, private intervenor Gensia Sicor Pharmaceuticals, Inc. and Bedford Laboratories, to market and sell generic forms of Sigma-Tau's levocarnitine drug. The agency approved the generics for the treatment of patients with inborn metabolic disorders, the unprotected indication. The generics compete with Carnitor.

As a result of these generic drug approvals, Sigma-Tau brought suit against the FDA on May 10, 2001. Sigma-Tau sought to have the approvals rescinded, or, in the alternative, to have the FDA change the generics' labeling to protect Sigma-Tau's orphan exclusivity. Sigma-Tau submits that the generics were in fact intended for use in patients with ESRD who are undergoing dialysis, and that they thereby infringed on the seven-year period of orphan exclusivity that Carnitor currently enjoys under the ODA.

The plain language of the ODA is unambiguous, and the FDA's approvals of the generics in this case comported with the clear wording of the statute. It is apparent that the FDA did not "approve another application ... for such drug for such disease or condition" here, but rather approved "another application ... for such drug" for a different disease or condition, one that was no longer subject to exclusivity. That is, the agency approved generic versions of Sigma-Tau's levocarnitine drug for people with inborn metabolic disorders, for which the period of orphan exclusivity had expired. The FDA did not approve the generics for the treatment of ESRD patients.

By using the words "such drug for such disease or condition," Congress made clear its intention that § 360cc(a) was to be disease-specific, not drug-specific. In other words, the statute as written protects uses, not drugs for any and all uses.

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. But this point is unavailing.

The evidentiary basis for the agency's approvals must be the use for which the approvals are sought – that is, the use for which the generics are labeled. The FDA necessarily approves the generics before their manufacturers engage in any actual marketing. If we were to ignore the deference due the FDA and impose exacting evidentiary standards upon its generic drug approval process, the agency would be faced with formidable problems. This is because many of the sources of evidence and market data to which Sigma-Tau points cannot be effectively analyzed in the pre-approval context. Thus, the intended-use inquiry Sigma-Tau urges upon us might evolve into a foreseeable-use test. Then, once the FDA approved an orphan drug

for a protected indication, generic competitors might be prohibited from entering the market for almost any use.

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 longstanding 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.

C Drug Marketing

Even after approval, the regulatory regime for dugs 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.

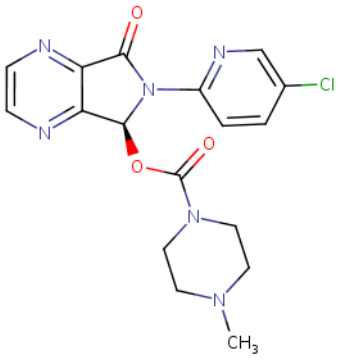
1 Names

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.

Note on Drug Naming

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 following molecular structure shown in the margin. It has the molecular formula $C_{17}H_{17}ClN_6O_3$, but the molecular formula is a poor name, because it is far from unique. Many other organic compounds also have seventeen carbon atoms, seventeen hydrogens, a chlorine, a nitrogen, and six oxygens. Instead, here are some of the names this molecule goes by:

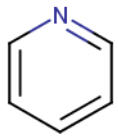


A chemical

- *IUPAC Name*: 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 name is derived by systematically listing each component of the

molecule, one at a time. Here, for example, `5-chlorpoyridine-2-yl` describes the ring at the right of the molecule, with the `5` specifying where the chlorine atom is attached to it and the `2` specifying where it is attached to the rest of the molecule. The *Nomenclature* describes in exacting detail the components, their names, the order to list them in, and the various numbers, hyphens, and other connectives that explain the components' relationship in the molecule. In trademark terms, the IUPAC name describes the molecule's structure and is intended to serve as a generic term for it.

- *InChI*: The IUPAC name contains components like `chlorpoyridine` that reflect the history of the common names people gave to molecules and their parts: `pyridine` is the nitrogen ring by itself. These common names don't directly reflect the underlying structure, so translating them back into the structure requires a great deal of knowledge about the different components and their names. The IUPAC has also promulgated a system, called InChI (short for "International Chemical Identifier") for converting molecular structures into more completely explicit descriptions that can be more straightforwardly converted back. The InChI for this molecule is `InChI=1S/C17H17ClN6O3/c1-22-6-8-23(9-7-22)17(26)27-16-14-13(19-4-5-20-14)15(25)24(16)12-3-2-11(18)10-21-12/h2-5,10,16H,6-9H2,1H3/t16-/m0/s1`. The InChI individually names each atom in the molecule, so it is longer, but also a little more transparent – which makes it easier for computers to reason about molecular structure. (A similar but somewhat less rigorous description system called SMILES would describe the molecule as `CN1CCN(CC1)C(=O)OC2C3=NC=CN=C3C(=O)N2C4=NC=C(C=C4)Cl`.) The InChI also describes the molecule's structure and is intended to serve as a generic term for it.



Pyridine

- *CAS Registry Number*: IUPAC names and InChIs are long and can be unwieldy – imagine transcribing an InChI trying to make sure you had each digit right, or glancing at two IUPAC names to see whether they were the same. The Chemical Abstracts Service, operated by the American Chemical Society (the leading professional organization for chemists in the United States) maintains an index of molecules that operates on very different principles. Each molecule in the index has a systematic name given according to the system *Naming and Indexing of Chemical Substances for Chemical Abstracts* published by the CAS – very much like the IUPAC system but only 156 pages and different in some respects – but also an index number, which has no chem-

ical significance, i.e. bears no relationship to the molecule's structure. Nonetheless, it is still intended to serve as a generic term for the molecule: anyone who looks up *138729-47-2* in the CAS Registry will find the molecular diagram and its systematic name, along with much more information about it. Because they are short, CAS Registry numbers are easier to read aloud and recognize at a glance; they are also commonly used in computer databases of chemicals. CAS Registry Numbers are assigned by the CAS; one must submit an application and pay a fee to obtain one. But as just noted, they are not "owned" by the applicant; the point is to make information about the chemical available to all (useful, for example, if one would like to advertise and sell a new compound one has just formulated).

- *InChIKey*: An interesting hybrid of the InChI and CAS Registry Number is the InChIKey. Take an InChI, and then run it through a hashing algorithm (specified by IUPAC) to yield a unique string of letters and numbers with a fixed length and format. This string has no chemical meaning, just like a CAS Registry Number. But it is decentralized like an InChI: anyone can come up with one. This molecule's InChIKey is `GBBSUAFBMRNDJC-INIZCTEOSA-N`.
- *Adopted Name*: All of these chemical names aren't particularly meaningful to humans. So 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, which is sponsored by the American Medical Association, the United States Pharmacopeial, and the American Pharmacists Association, and collaborates with the FDA. 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 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.

  4. A name should be free from conflict with other nonproprietary names and with established trademarks and should

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

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."

New adopted names are subject to a long list of specific requirements, such as that "the letter 'f' should be used instead of 'ph'." The USAN Council publishes a list of adopted names, and it also works with the applicant to forward proposed adopted names to the World Health Organization for inclusion in its own International Nonproprietary Names index. As the names of this type of name suggest, it too is meant to be generic in the sense that anyone is free to use the name to refer to the chemical – but notice how trademark considerations are starting to creep into the choice of names. 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). (Here is the USAN Council's statement on eszopiclone.)

- *Established Name*: The FDA considers some names to be "established names" for drugs – 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. `aspirin` is an example.

See 21 C.F.R. § 299.4

- *Proprietary Name*: 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. The FDA will then engage 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

Are the following the names of drugs or of elves?

- Frova
- Erestor
- Isentress
- Qvar
- Celeborn
- Oropher

See Which Is It: Prescription Drug or Tolkien Elf? at How Stuff Works: Entertainment

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 that the trademark likelihood of confusion analysis. The FDA will compare the proposed name against its Phonetic and Orthographic Computer Analysis 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.

Senate Report No. 448, 87th Congress, 1st Session (1961)
Administered Prices--Drugs

In addition to patent controls and the vast amounts spent on advertising and promotion, the control of the market by the large drug companies stems from a third source of power; this is their remarkable success in persuading physicians to prescribe by trade names rather than generic names. Where this is done the small manufacturer is automatically excluded from the market, regardless of whether the drugs are patented or non-patented, and the opportunity for price competition disappears. This state of affairs is furthered by anything which causes the physician to be apprehensive of, or have difficulty in, prescribing by generic names.

The multiplicity of names' for products in the drug industry virtually exceeds the bounds of human imagination. First, there is the chemical name which attempts to spell out the structural makeup of the drug; and here a variety of forms of expression is possible. Next comes the generic name which may or may not represent an abbreviation of the more complex chemical name; this is the name commonly used to identify the drug in formularies, the teaching of medicine, etc. Ordinarily a drug has one generic name, but there are cases where two or three are employed. Finally a drug usually has a host of individual trade names used by the various companies engaged in the promotion of the product. In consequence, a single drug product is represented in the market by such complex body of nomenclature as

to intimidate even the initiates in the field. And if one can visualize this situation for a single drug multiplied by the thousands of drugs currently marketed, he can get some impression of the chaos existing in the area of drug nomenclature.

The new so-called synthetic penicillin illustrates the problem. The chemical name for this product is alpha-phenoxyethyl penicillin potassium. This set of syllables is also used as a generic name. In addition, there are two other generic names – potassium penicillin 152 and phenethicillin potassium. Since the product is protected by patent, there are only six sellers, each of whom markets under his own trade name. Thus the prescribing physician is bombarded with promotional material for Syncillin, Darcil, Alpen, Chemipen, Dramcillin-S, and Maxipen. All of these are, of course, the same chemical compound.

Speaking of them, Dr. Walter Modell, professor of pharmacology and therapeutics at Cornell University Medical College, stated:

> They are colored differently (pink, peach, green, and two shades of yellow) and are advertised as distinctive materials but no effort is made in promotional material to inform the physician who is urged to use them that they are otherwise identical.

In this example the busy practitioner is confronted with three generic names, six brand names used as the name of the drug itself, and at least five different colors. Thus, there are 14 different identification symbols for the identical drug. In terms of nomenclature, each product stands isolated; indeed, there is an attempt to conceal the identical nature of the drug.

Code of Federal Regulations

Drugs; statement of ingredients
21 C.F.R. § 201.10(g)

(1) If the label or labeling of a prescription drug bears a proprietary name or designation for the drug or any ingredient thereof, the established name, if such there be, corresponding to such proprietary name or designation shall accompany such proprietary name or designation ...

(2) The established name shall be printed in letters that are at least half as large as the letters comprising the proprietary name or designation with which it is joined, and the established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features.

369 F.3d 700 (3d Cir. 2004)

Kos Pharmaceuticals, Inc. v. Andrx Corp.

On October 3, 2000, Kos filed an application with the PTO to register ADVICOR as the mark for a new medication designed to improve cholesterol levels. This new drug combines 20 milligrams of lovastatin (which lowers LDL, or "bad" cholesterol) with varying strengths (500, 750, or 1000 milligrams) of an extended-release formulation of niacin (which increases HDL, or "good" cholesterol). Kos has been selling its proprietary extended-release form of niacin under the trade name Niaspan since 1997. In July 2001 Kos began advertising, and in December 2001 began selling, its new combination drug, Advicor.

Shortly after Kos began marketing Advicor, it learned that Andrx planned to use the mark ALTOCOR for its own new anticholesterol medication, which would contain only a single active ingredient, an extended-release form of lovastatin, in varying strengths (10, 20, 40 or 60 milligrams). Andrx announced on January 31, 2002 that it had received preliminary marketing approval for Altocor from the FDA. On February 5, 2002, the PTO published for opposition the ALTOCOR mark, which Andrx had applied to register in December 2000.

Kos tried to dissuade or otherwise prevent Andrx from using the ALTOCOR mark several times, both before and after Andrx began selling its new drug. Kos also expressed its concerns about potential confusion to the FDA division responsible for reviewing proposed new drug names from a public health perspective, the Office of Drug Safety's Division of Medication Errors and Technical Support. The Division of Medication Errors had preliminarily approved the name Altocor in November 2001. At that time, the Division stated that the "name Advicor looks and sounds similar to Altocor," but concluded that the "difference in the written strengths" of the drugs reduced the risk of "error ... between the two products."

The parties submitted competing medical affidavits to support their respective views as to the nature and severity of potential consequences of mis-filled prescriptions. Per Kos, niacin – and thus Advicor, but not Altocor – may cause serious injury, or even death, to patients with various conditions or sensitivities to the drug. Other, less serious, side effects of niacin may worry patients who have not been warned of those effects, and who may thus discontinue needed treatment. Patients who mistakenly receive Altocor rather than Advicor are also at risk, says Kos, since the conditions the niacin is meant to address will remain untreated. Andrx, on the other hand, claims that the "safety profile of both products is similar" and that there need not be "any unusual concern" about "harm to the public if the Andrx product is substituted for the KOS product."

[The District Court denied a preliminary injunction. The Court of Appeals reversed. The excerpts that follow focus on the relationship between the FDA's consideration of the proposed name and the likelihood of confusion inquiry under the Lanham Act.]

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 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

[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.

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 erroneous.

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.

666 Problem

In *United States v. 70 1/2 Dozen Bottles, and 76 1/2 Dozen Bottles of "666"*, 1938-1964 FDLI Jud. Rec. 89 (M.D. Ga. 1944), the Monticello Drug Company had sold a product containing quinine under the name "666". During World War II, the supply of quinine was restricted and Monticello stopped putting it in 666. It was seized and destroyed as a "misbranded drug" under the theory that keeping the same name and trade dress would mislead consumers into "accepting the new

Bottle of 666, date unknown.

product under the impression that they were obtaining the old product." Is this theory sound? Is it consistent with what you know of trademark law?

2 Design

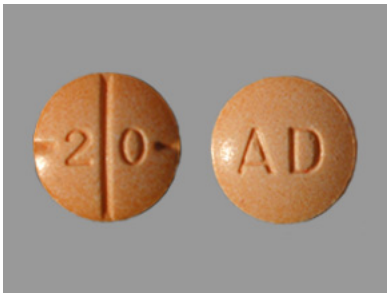
One might expect the law of drug trade dress to track the law of drug names closely. One would be wrong.

Shire US Inc. v. Barr Laboratories, Inc.

329 F.3d 348 (3d Cir. 2003)

Adderall is a central nervous system stimulant used in treating attention deficit hyperactivity disorder (ADHD) available only by prescription and dispensed to patients in pharmacy vials labeled "prescription-only" as required by law. Adderall is composed of the mixed salts of a single-entity amphetamine and is a controlled substance. Shire first placed Adderall on the market in 1996 and since that time it has enjoyed substantial success so that by 2001 it had a 32% market share in the United States ADHD prescription market.

Adderall originally came in two dosage strengths and colors, 10 mg. (blue, round) and 20 mg. (orange, round). 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.



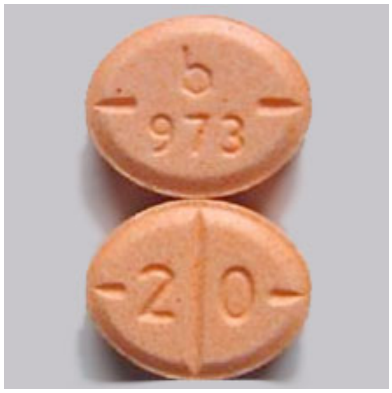
Shire 20mg Adderall mixed amphetamine salts

Shire's product literature, promotional materials, and mailings, which its sales staff distributed to physicians, feature color pictures of the Adderall tablets and sometimes direct patients to examine the tablets to ensure that they have received exactly the drug prescribed. Shire does not advertise its products in general consumer publications, but pictures of Adderall tablets appear in the Physician's Desk Reference and in certain consumer books. While Shire continues to sell Adderall, it altered its marketing strategy for 2002 and discontinued promoting Adderall, promoting instead a patented, sustained-release version of the drug, Adderall XR.

Barr, a public company that develops and manufactures generic and proprietary pharmaceuticals, was the first manufacturer of a generic equivalent to Adderall. It began developing a generic amphetamine salt alternative in 1998 and started marketing it in February 2002 after submitting an ANDA" to the FDA and obtaining its approval. The FDA has approved Barr's generic amphetamine salts as safe and effective, and has classified Barr's product, which it manufactures in accordance with FDA regulations, as therapeutically equiva-

lent to Adderall. Barr's product is the bioequivalent of Adderall, for which it thus may be interchanged freely. According to Shire, however, the products contain different inactive ingredients, and, in particular, Barr's tablets contain saccharin, a once controversial ingredient the FDA only recently removed from its list of banned substances.

Barr manufactures its generic amphetamine salts in 5 mg. (blue, oval), 10 mg. (blue, oval), 20 mg. (orange/peach, oval), and 30 mg. (orange/peach, oval) tablets.[4] 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."



Barr 20mg mixed amphetamine salts

On April 30, 2002, Shire filed this action against Barr, alleging that Barr's sale of generic amphetamine salts copying Adderall's appearance constituted unfair competition and diluted Shire's rights under federal and state law. The district court found that Shire "has not credibly rebutted Barr's theory that the similar color-coding and shape of the products are particularly meaningful for ADHD patients and enhance efficacy" [and thus are functional].

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

[4]For Barr's product to be approved as a generic equivalent for Adderall, it was required to produce the same dosage strengths available for Adderall. Shire, however, launched its mid-range dosages (7.5 mg., 12.5 mg. and 15 mg.) after Barr filed its ANDA with the FDA. In an internal memorandum, Shire indicated that its motivation for introducing these new strengths was to "buy time" to protect market share because generic substitutes would not be available for all strengths, thereby minimizing competition from substitutes.

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."

Most of the opinions on which Shire relies were district court opinions from the early 1980s[14] which the court here was not bound to follow. In addition, the cases on which Shire relies are distinguishable on their facts.

Most significantly, though the cases involved prescription drugs, none involved controlled substances and in all of the cases there was evidence of the passing off of the defendant's product by pharmacists, or of an intent to induce illegal substitution on the defendant's part.

SK&F: 625 F.2d 1055 (3d Cir. 1980)

It is true that in several of the cases on which Shire relies, the defendant offered affidavits and declarations of pharmacists and physicians making claims relating to functionality that the courts in those cases did not credit the evidence. For example, in *SK&F, Co. v. Premo Pharmaceutical Lab.*, Dr. Shafer, a physician, submitted an affidavit in which he supported the sale of similarly configured generic tablets as he believed this configuration would enable the patient to feel confident that there was no change in the chemistry of the medication and that patients might become uneasy, confused or react adversely if the generic medication looked different from the market innovator. But we explained that the district court nevertheless "apparently chose not to credit the assertion of the Shafer affidavit, crediting instead the affidavits of Drs. Meyerson and Tannenbaum that in their experience the appearance of a drug bears no established relationship to its therapeutic efficacy." Just as in *SK&F* we deferred to the district court's findings of fact it is appropriate for us to do so in this case as well.

While district courts in this circuit have rejected functionality ar-

[14]Those cases were decided prior to: (1) the enactment in 1984 of the Hatch-Waxman amendment, which established a federal policy favoring the marketing of therapeutic equivalents of generic drugs, (2) the 1999 amendment to 15 U.S.C. § 1125(a)(3) which places the burden of proving non-functionality of unregistered trade dress on the plaintiff, and (3) the Supreme Court's decisions in *Wal-Mart* and *TrafFix*.

guments similar to those the court credited in this case, other district courts, such as that in *Ives Laboratories, Inc. v. Darby Drug Co.*[19], have credited similar testimony bearing on functionality. In *Ives* the manufacturer of the prescription drug cyclandelate sought an injunction against manufacturers of generic cyclandelate claiming that the defendants' use of the same capsule colors was "a false designation of origin" or a "false description or representation" of defendants' product. But the district court in *Ives* found that capsule colors were functional in several respects. "First, many elderly patients associate the appearance of their medication with its therapeutic effect. Second, some patients co-mingle their drugs in a single container and then rely on the appearance of the drug to follow their doctors' instructions. Third, to some limited extent color is also useful to doctors and hospital emergency rooms in identifying overdoses of drugs."

Ives: 488 F. Supp. 394 (E.D.N.Y. 1980)

Jeremy A. Greene & Aaron S. Kesselheim

Why Do the Same Drugs Look Different? Pills, Trade Dress, and Public Health

365 New Eng. J. Med. 83 (2011)

Protection of intellectual property covering the physical attributes of pills therefore served two primary purposes. One purpose of trade-dress protection was to reduce the practice of palming off. Premo Pharmaceuticals was sued for trade-dress infringement when it marketed its generic version of the diuretic hydrochlorothiazide/triamterene with a maroon-and-white capsule identical to that of brand-name drug Dyazide, produced by Smith, Kline and French. In *SK&F*, the Third Circuit Court of Appeals upheld trade-dress protection because near-identical pills would facilitate the practice of "unscrupulous pharmacists" in "substituting less expensive generic drugs for the brand name drugs prescribed without informing their customers and without passing along the benefit of the lower price." The court also found that the color scheme was nonfunctional because it did not help patients identify the drug, pointing to other maroon-and-white capsules that were not diuretics.

A second purpose, the courts rationalized, was to allow trade-dress protection to serve a public health function by preventing the substitution of a drug that was similar but not identical to another. In *SK&F*, the two diuretic products were chemically equivalent, but their rate of absorption into the bloodstream (bioavailability) differed. In another case, a federal district court in Michigan enjoined a competitor from producing a version of the diet pill phentermine that was similar in appearance to a brand-name version because the efficacy of

[19]The court of appeals reversed in *Ives*, but the Supreme Court in turn reversed the court of appeals in *Inwood Laboratories, Inc. v. Ives Laboratories, Inc.*

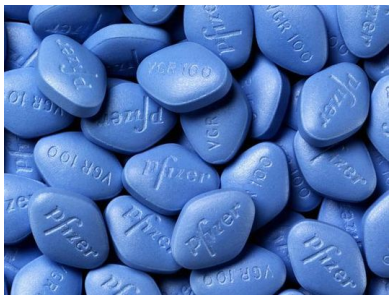
the hydrochloride salt of phentermine in the generic manufacturer's version did not necessarily match the efficacy of the brand-name manufacturer's phentermine resin complex, so the two drugs were not interchangeable. *Pennwalt v. Zenith Laboratories*. Notably, both these arguments upholding pharmaceutical trade-dress rights were meant to protect consumers from deception by the producers of look-alike drugs.

Pennwalt: 472 F.Supp. 413 (E.D. Mich. 1979)

AstraZeneca's omeprazole (Prilosec) was widely promoted as "the purple pill" after its launch in 1989. As Prilosec's market exclusivity was ending, AstraZeneca launched the prescription-only follow-on product esomeprazole (Nexium) as "the new purple pill" in 2001 to encourage patients accustomed to taking Prilosec to switch to Nexium. Notably, when AstraZeneca began to sell omeprazole without a prescription as Prilosec OTC, the company changed the color of its product to salmon pink. Conversely, as Lilly's green-and-cream capsule fluoxetine (Prozac, 20 mg) faced generic-drug competition in 2001, the company repackaged fluoxetine in pink-and-purple capsules and marketed it as a new drug, Sarafem (20 mg), which was approved by the FDA in 2000 for the treatment of a new indication – perimenstrual dysphoric disorder. In this case, the change in color was designed to discourage physicians from prescribing the less expensive generic fluoxetine in place of Sarafem.

Image from AstraZeneca website at purplepill.com

Nexium capsules



Viagra tablet

The 1997 FDA guidelines for expanding direct-to-consumer (DTC) advertising of prescription drugs further enhanced the power of pharmaceutical trade dress as broadcast campaigns began to include images of the pills themselves. One of the first drugs to be promoted heavily to consumers after its approval in 1998 was Viagra (sildenafil), Pfizer's drug for treating erectile dysfunction. The company included a picture of the drug in nearly all the advertisements for it, which served to identify the brand of Viagra with both the color (pale blue) and the shape (diamond) of the tablets.

[Despite *Shire*,] claims of trade dress remain vital in the pharmaceutical market. With increasing generic competition, trade-dress strategies are described in industry publications as ways for innovator firms to retain market share for their products after their patents and market exclusivity expire. During at least the past 5 years, brand-name pharmaceutical companies have begun to license their trade dress to manufacturers of so-called authorized generics, which advertise the characteristic of similar appearance as a reason for consumers to use these products.

If brand-name pharmaceutical manufacturers are no longer able to rely on trade dress to protect the attributes of their products, federal policies affecting this field need to be sharply reconsidered. A first step toward reform would be to include FDA certification of pharmaceutical size, shape, and color in the drug-approval process.

For example, a pill's attributes could be proposed by the manufacturer during the original New Drug Application. Currently, such a process occurs for the brand name of the medication; extending it to pill appearance should not require additional legislation. This would create a clear path for generic manufacturers to declare during the ANDA process that their products have similar appearances. Where these drugs do differ (e.g., as in dyes, fillers, or excipients), physicians or pharmacists could still locate manufacturer data from unique identifier codes embossed on pills. Further public health benefits could emerge if the reduction in trade dress helps to combat the physician's persistent use of, and the patient's preference for, costly brands when generic equivalents are available.

The obvious limitation of this approach is that it would apply only to newly introduced pharmaceutical products, leaving most of the existing therapeutic armamentarium unaffected. Therefore, we suggest that a rational scheme be created for pharmaceuticals that have already been approved whereby each distinct agent could be identified by a combination of its size, shape, and color. An example of such a scheme is the successful introduction in the United Kingdom of color-coding for metered-dose inhalers. Patients with asthma had frequently confused bronchodilators with steroid inhalers, leading the National Health Service to systematize inhaler appearance: all short-acting inhalers (bronchodilators) became blue and all preventive agents (steroids) became brown, orange, or burgundy. A similar color-coding scheme was piloted in the United States for ophthalmologic products, in which the caps on generic preparations of atropine, pilocarpine, and other drug products having multiple strengths were color-coded to match those of the innovator-drug products.

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 form using them.) These rules depart – in several fairly significant ways – from the usual general rules for false advertising. 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. Is it any surprise that legally mandated copying raises intellectual property issues?

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 broad-

cast 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" . The resulting information disclosure is commonly called the *brief summary*.

21 U.S.C. § 352(n)

21 CFR § 202.1

The prescription drug advertising regulations 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*.

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". 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.

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 healthcare 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 lan-

guage.

A sponsor wishing to use consumer-directed broadcast advertisements 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. These violations are concerning from a public health perspective because they suggest that DICLEGIS is safer than has been

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

demonstrated.

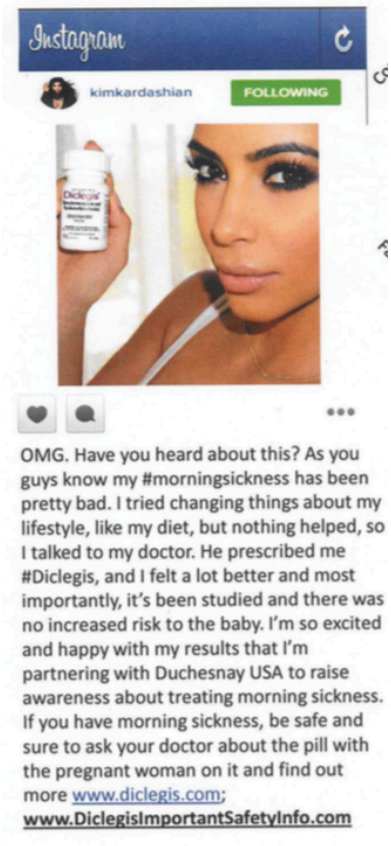
According to its FDA-approved product labeling (PI) (emphasis in original):

> 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 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 challenged Kim Kardashian Social Media Post

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 in-

dication, 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.

United States v. Caronia

703 F.3d 149 (2d Cir. 2012)

Under the Federal Food, Drug and Cosmetic Act, before drugs are distributed into interstate commerce, they must be approved by the FDA for specific uses. To obtain FDA approval, drug manufacturers are required to demonstrate, through clinical trials, the safety and efficacy of a new drug for each intended use or indication.

Once FDA-approved, prescription drugs can be prescribed by doctors for both FDA-approved and -unapproved uses; the FDA generally does not regulate how physicians use approved drugs. Indeed, courts and the FDA have recognized the propriety and potential public value of unapproved or off-label drug use. Off-label use is an accepted and necessary corollary of the FDA's mission to regulate in this area without directly interfering with the practice of medicine. FDA-approved indications were not intended to limit or interfere with the practice of medicine nor to preclude physicians from using their best judgment in the interest of the patient.The FDA itself has observed:

> Once a drug has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such "unapproved" or, more precisely, "unlabeled" uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in medical literature.

The FDCA prohibits "misbranding." A drug is misbranded if, *inter alia*, its labeling fails to bear "adequate directions for use,", which FDA regulations define as "directions under which the lay[person] can use a drug safely and for the purposes for which it is intended."[3] FDA regulations define intended use by reference to "the objective intent of the persons legally responsible for the labeling of drugs," which may be demonstrated by, among other evidence, "oral or written statements by such persons or their representatives" and "the cir-

21 U.S.C. § 352(f)

21 C.F.R. § 201.5

[3] A drug is also misbranded if, *inter alia*: its label is false or misleading; the label fails to display required information prominently; its container is misleading; or it is dangerous to health when used in the dosage, manner, frequency, or duration prescribed, recommended, or suggested on the label.

21 C.F.R. § 201.128.

cumstances that the article is, with the knowledge of such persons or their representatives, offered and used for a purpose for which it is neither labeled nor advertised."

The consequences for misbranding are criminal. Pharmaceutical manufacturers and their representatives can face misdemeanor charges for misbranding or felony charges for fraudulent misbranding. The government has repeatedly prosecuted – and obtained convictions against – pharmaceutical companies and their representatives for misbranding based on their off-label promotion. The FDCA and its accompanying regulations do not expressly prohibit the "promotion" or "marketing" of drugs for off-label use. The regulations do recognize that promotional statements by a pharmaceutical company or its representatives can serve as proof of a drug's intended use. Off-label promotional statements could thus presumably constitute evidence of an intended use of a drug that the FDA has not approved. The FDA, however, has concluded that "an approved drug that is marketed for an unapproved use (whether in labeling or not) is misbranded because the labeling of such drug does not include 'adequate directions for use.'" Thus, the government has treated promotional speech as more than merely evidence of a drug's intended use – it has construed the FDCA to prohibit promotional speech as misbranding itself.

Orphan Medical manufactured the drug Xyrem, a powerful central nervous system depressant. Xyrem can cause serious side effects, including difficulty breathing while asleep, confusion, abnormal thinking, depression, nausea, vomiting, dizziness, headache, bedwetting, and sleepwalking. If abused, Xyrem can cause additional medical problems, including seizures, dependence, severe withdrawal, coma, and death. Xyrem's active ingredient is gamma-hydroxybutryate ("GHB"). GHB has been federally classified as the "date rape drug" for its use in the commission of sexual assaults.

Despite the risks associated with Xyrem and GHB, the FDA approved Xyrem for two medical indications. In July 2002, the FDA approved Xyrem to treat narcolepsy patients who experience cataplexy, a condition associated with weak or paralyzed muscles. In November 2005, the FDA approved Xyrem to treat narcolepsy patients with excessive daytime sleepiness ("EDS"), a neurological disorder caused by the brain's inability to regulate sleep-wake cycles.

Caronia was audio-recorded on two occasions as [he] promoted Xyrem for unapproved uses, including unapproved indications [including chronic fatigue chronic pain, and restless leg] and unapproved subpopulations [patients under 16]. He was found guilty of conspiracy to introduce a misbranded drug into interstate commerce.

On appeal, Caronia principally argues that the misbranding provisions of the FDCA prohibit off-label promotion, and therefore, un-

constitutionally restrict speech. Caronia argues that the First Amendment does not permit the government to prohibit and criminalize a pharmaceutical manufacturer's truthful and non-misleading promotion of an FDA-approved drug to physicians for off-label use where such use is not itself illegal and others are permitted to engage in such speech.

As off-label drug use itself is not prohibited, it does not follow that prohibiting the truthful promotion of off-label drug usage by a particular class of speakers would directly further the government's goals of preserving the efficacy and integrity of the FDA's drug approval process and reducing patient exposure to unsafe and ineffective drugs. Prohibiting off-label promotion by a pharmaceutical manufacturer while simultaneously allowing off-label use "paternalistically" interferes with the ability of physicians and patients to receive potentially relevant treatment information; such barriers to information about off-label use could inhibit, to the public's detriment, informed and intelligent treatment decisions. In fact, in granting safe harbor to manufacturers by permitting the dissemination of off-label information through scientific journals, the FDA itself recognizes that public health can be served when health care professionals receive truthful and non-misleading scientific and medical information on unapproved uses of approved drugs.

If the government is concerned that off-label promotion may mislead physicians, it could guide physicians and patients in differentiating between misleading and false promotion, exaggerations and embellishments, and truthful or non-misleading information. The government could develop its warning or disclaimer systems, or develop safety tiers within the off-label market, to distinguish between drugs. The government could require pharmaceutical manufacturers to list all applicable or intended indications when they first apply for FDA approval, enabling physicians, the government, and patients to track a drug's development. To minimize off-label use, or manufacturer evasion of the approval process for such use, the government could create other limits, including ceilings or caps on off-label prescriptions. The FDA could further remind physicians and manufacturers of, and even perhaps further regulate, the legal liability surrounding off-label promotion and treatment decisions.[11] Finally, where off-label drug use is exceptionally concerning, the government could prohibit the off-label use altogether.

Accordingly, even if speech can be used as evidence of a drug's intended use, we decline to adopt the government's construction of the FDCA's misbranding provisions to prohibit manufacturer promotion alone as it would unconstitutionally restrict free speech. We construe the misbranding provisions of the FDCA as not prohibiting and criminalizing the truthful off-label promotion of FDA-approved pre-

scription drugs.

Wyeth v. Levine

129 S. Ct. 1187 (2009)

Phenergan is Wyeth's brand name for promethazine hydrochloride, an antihistamine used to treat nausea. The injectable form of Phenergan can be administered intravenously through either the "IV-push" method, whereby the drug is injected directly into a patient's vein, or the "IV-drip" method, whereby the drug is introduced into a saline solution in a hanging intravenous bag and slowly descends through a catheter inserted in a patient's vein. The drug is corrosive and causes irreversible gangrene if it enters a patient's artery.

Diana Levine's injury resulted from an IV-push injection of Phenergan. Phenergan entered Levine's artery, either because the needle penetrated an artery directly or because the drug escaped from the vein into surrounding tissue (a phenomenon called "perivascular extravasation") where it came in contact with arterial blood. As a result, Levine developed gangrene, and doctors amputated first her right hand and then her entire forearm. In addition to her pain and suffering, Levine incurred substantial medical expenses and the loss of her livelihood as a professional musician. Although Phenergan's labeling warned of the danger of gangrene and amputation following inadvertent intra-arterial injection, Levine alleged that the labeling was defective because it failed to instruct clinicians to use the IV-drip method of intravenous administration instead of the higher risk IV-push method.

The question presented is whether federal law pre-empts Levine's claim that Phenergan's label did not contain an adequate warning about using the IV-push method of administration.

Wyeth and *PLIVA* are technically failure-to-warn products liability cases. But if you think of an "adequate warning" as a statement required to make a product's label not misleading, they have a lot in common with false advertising law.

Wyeth first argues that Levine's state-law claims are pre-empted because it is impossible for it to comply with both the state-law duties underlying those claims and its federal labeling duties. The FDA's premarket approval of a new drug application includes the approval of the exact text in the proposed label. Generally speaking, a manufacturer may only change a drug label after the FDA approves a supplemental application. There is, however, an FDA regulation that permits a manufacturer to make certain changes to its label before receiving the agency's approval. Among other things, this "changes being effected" (CBE) regulation provides that if a manufacturer is changing a label to "add or strengthen a contraindication, warning, precaution, or adverse reaction" or to "add or strengthen an instruction about dosage and administration that is intended to increase the safe use of the drug product," it may make the labeling change upon filing its supplemental application with the FDA; it need not wait for FDA approval.

Wyeth suggests that the FDA, rather than the manufacturer, bears

primary responsibility for drug labeling. Yet through many amendments to the FDCA and to FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the market. Of course, the FDA retains authority to reject labeling changes made pursuant to the CBE regulation in its review of the manufacturer's supplemental application, just as it retains such authority in reviewing all supplemental applications. But absent clear evidence that the FDA would not have approved a change to Phenergan's label, we will not conclude that it was impossible for Wyeth to comply with both federal and state requirements.

PLIVA, Inc. v. Mensing

131 S. Ct. 2567 (2011)

Metoclopramide is a drug designed to speed the movement of food through the digestive system. The Food and Drug Administration (FDA) first approved metoclopramide tablets, under the brand name Reglan, in 1980. Five years later, generic manufacturers also began producing metoclopramide. The drug is commonly used to treat digestive tract problems such as diabetic gastroparesis and gastroesophageal reflux disorder. Evidence has accumulated that long-term metoclopramide use can cause tardive dyskinesia, a severe neurological disorder. Accordingly, warning labels for the drug have been strengthened and clarified several times [in 1985, 2004, and 2009].

Gladys Mensing and Julie Demahy, the plaintiffs in these consolidated cases, were prescribed Reglan in 2001 and 2002, respectively. Both received generic metoclopramide from their pharmacists. After taking the drug as prescribed for several years, both women developed tardive dyskinesia.

In separate suits, Mensing and Demahy sued the generic drug manufacturers that produced the metoclopramide they took. Each alleged, as relevant here, that long-term metoclopramide use caused her tardive dyskinesia. Mensing and Demahy have pleaded that the Manufacturers knew or should have known of the high risk of tardive dyskinesia inherent in the long-term use of their product. They have also pleaded that the Manufacturers knew or should have known that their labels did not adequately warn of that risk. The parties do not dispute that, if these allegations are true, state law required the Manufacturers to use a different, safer label.

Federal law imposes far more complex drug labeling requirements. [Under Hatch-Waxman,] brand-name and generic drug manufacturers have different federal drug labeling duties. A brand-name manufacturer seeking new drug approval is responsible for the accuracy and adequacy of its label. A manufacturer seeking generic drug

approval, on the other hand, is responsible for ensuring that its warning label is the same as the brand name's.

According to the FDA, the Manufacturers could have proposed – indeed, were required to propose – stronger warning labels to the agency if they believed such warnings were needed. If the FDA had agreed that a label change was necessary, it would have worked with the brand-name manufacturer to create a new label for both the brand-name and generic drug.

Where state and federal law directly conflict, state law must give way. We have held that state and federal law conflict where it is impossible for a private party to comply with both state and federal requirements.

We find impossibility here. It was not lawful under federal law for the Manufacturers to do what state law required of them.

If the Manufacturers had independently changed their labels to satisfy their state-law duty, they would have violated federal law. Taking Mensing and Demahy's allegations as true, state law imposed on the Manufacturers a duty to attach a safer label to their generic metoclopramide. Federal law, however, demanded that generic drug labels be the same at all times as the corresponding brand-name drug labels. Thus, it was impossible for the Manufacturers to comply with both their state-law duty to change the label and their federal law duty to keep the label the same.

In 2013, the FDA announced a complex proposed rule to allow generics to update their labels. As of 2016, the final rule was still pending.

The federal duty to ask the FDA for help in strengthening the corresponding brand-name label, assuming such a duty exists, does not change this analysis. Although requesting FDA assistance would have satisfied the Manufacturers' federal duty, it would not have satisfied their state tort-law duty to provide adequate labeling. State law demanded a safer label; it did not instruct the Manufacturers to communicate with the FDA about the possibility of a safer label.

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 competing 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. Thus, Watson's generic nicotine gum was accompanied by a user guide and audio tape that were virtually identical to SmithKline's.

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 FFDCA 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.