Biotechnology

11

Biotechnology

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. 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 not 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 Patent

1 Subject Matter

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

[According to the Supreme Court's summary, human DNA consists of a long string of nucleotides, each of which is one of four molecular fragments commonly abbreviated A, C, T, and G. Each sequence of three nucleotides codes for one of twenty amino acids, the molecules from which the body builds proteins. A gene is sequence of nucleotides that code for the amino acids making up a protein; put another way, a gene contains the information the body uses to make a particular protein. Naturally occurring DNA sequences contain

portions, called "introns," that do not actually code for amino acids; those portions are ignored when the body makes proteins from genes. The remaining portions of DNA, which do code for amino acids and which are used in making proteins, are called "exons."

Myriad discovered that mutations in two human genes, BRCA1 and BRCA2, substantially increased a woman's risk of developing breast cancer. It developed and marketed a test for these mutations. It also obtained multiple patents related to the discovery and the test, which it used to prevent competition from other tests. Claim 1 of patent 5,747,282, for example, claimed "an isolated DNA coding for a BRCA1 polypeptide," with "the amino acid sequence set forth in [an attachment listing a sequence of 1,863 amino acids]." Other claims covered cDNA (short for "complementary DNA"), which is created using synthetic laboratory methods by copying naturally occurring DNA. The resulting molecule differs in that it contains only exons and omits the introns.]

It is undisputed that Myriad did not create or alter any of the genetic information encoded in the BRCA1 and BRCA2 genes. The location and order of the nucleotides existed in nature before Myriad found them. Nor did Myriad create or alter the genetic structure of DNA. Instead, Myriad's principal contribution was uncovering the precise location and genetic sequence of the BRCA1 and BRCA2 genes within chromosomes 17 and 13. The question is whether this renders the genes patentable.

Chakrabarty: 443 U.S. 303 (1980)

Myriad recognizes that our decision in *Diamond v. Chakrabarty* is central to this inquiry. In *Chakrabarty*, scientists added four plasmids to a bacterium, which enabled it to break down various components of crude oil. The Court held that the modified bacterium was patentable. It explained that the patent claim was "not to a hitherto unknown natural phenomenon, but to a nonnaturally occurring manufacture or composition of matter — a product of human ingenuity having a distinctive name, character and use." The Chakrabarty bacterium was new "with markedly different characteristics from any found in nature," due to the additional plasmids and resultant "capacity for degrading oil." In this case, by contrast, Myriad did not create anything. To be sure, it found an important and useful gene, but separating that gene from its surrounding genetic material is not an act of invention.

Groundbreaking, innovative, or even brilliant discovery does not by itself satisfy the § 101 inquiry.

Nor are Myriad's claims saved by the fact that isolating DNA from the human genome severs chemical bonds and thereby creates a nonnaturally occurring molecule. Myriad's claims are simply not expressed in terms of chemical composition, nor do they rely in any way on the chemical changes that result from the isolation of a par-

ticular section of DNA. Instead, the claims understandably focus on the genetic information encoded in the BRCA1 and BRCA2 genes. If the patents depended upon the creation of a unique molecule, then a would-be infringer could arguably avoid at least Myriad's patent claims on entire genes (such as claims 1 and 2 of the '282 patent) by isolating a DNA sequence that included both the BRCA1 or BRCA2 gene and one additional nucleotide pair. Such a molecule would not be chemically identical to the molecule "invented" by Myriad. But Myriad obviously would resist that outcome because its claim is concerned primarily with the information contained in the genetic sequence, not with the specific chemical composition of a particular molecule.

cDNA does not present the same obstacles to patentability as naturally occurring, isolated DNA segments. As already explained, creation of a cDNA sequence from mRNA results in an exons-only molecule that is not naturally occurring. Petitioners concede that cDNA differs from natural DNA in that "the non-coding regions have been removed." They nevertheless argue that cDNA is not patent eligible because "the nucleotide sequence of cDNA is dictated by nature, not by the lab technician." That may be so, but the lab technician unquestionably creates something new when cDNA is made. cDNA retains the naturally occurring exons of DNA, but it is distinct from the DNA from which it was derived. As a result, cDNA is not a "product of nature" and is patent eligible under § 101, except insofar as very short series of DNA may have no intervening introns to remove when creating cDNA. In that situation, a short strand of cDNA may be indistinguishable from natural DNA.

"The Court draws a distinction between unpatentable genomic DNA and patentable cDNA, but the difference between these two types of DNA lies in how they are made, not their sequence. A cDNA generated from an organism without introns (e.g. bacteria) will have the exact same sequence as genomic DNA. Furthermore, the splice junctions in human cDNA are natural: they were not designed by an inventor." Eric Grote, *Legal and Scientific Flaws in the Myriad Genetics Litigation* (unpublished draft 2014).

Justice SCALIA, concurring in part and concurring in the judgment.

I join the judgment of the Court, and all of its opinion except Part I-A and some portions of the rest of the opinion going into fine details of molecular biology. I am unable to affirm those details on my own knowledge or even my own belief. It suffices for me to affirm, having studied the opinions below and the expert briefs presented here, that the portion of DNA isolated from its natural state sought to be patented is identical to that portion of the DNA in its natural state; and that complementary DNA (cDNA) is a synthetic creation not normally present in nature.

In re Roslin Institute (Edinburgh)
750 F.3d 1333 (2014)

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.

Dolly the Sheep

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.

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

Even before the Supreme Court's recent decision in *Myriad*, the Court's opinions in *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 differences 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 frac-

tion 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 alternative 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. Be-

cause 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 MateriT21 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 metabolites 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.

Is Prancer a copyrightable work of authorship?

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!

2 Ownership

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

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

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.

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

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 antipsychotic 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 Defenses

Bowman v. Monsanto Co.
133 S. Ct. 1761 (2013)

Under the doctrine of patent exhaustion, the authorized sale of a patented article gives the purchaser, or any subsequent owner, a right to use or resell that article. Such a sale, however, does not allow the purchaser to make new copies of the patented invention. The question in this case is whether a farmer who buys patented seeds may reproduce them through planting and harvesting without the patent holder's permission. We hold that he may not.

I

Respondent Monsanto invented a genetic modification that enables soybean plants to survive exposure to glyphosate, the active ingredient in many herbicides (including Monsanto's own Roundup). Monsanto markets soybean seed containing this altered genetic material as Roundup Ready seed. Farmers planting that seed can use a glyphosate-based herbicide to kill weeds without damaging their crops. Two patents issued to Monsanto cover various aspects of its

Roundup Ready technology, including a seed incorporating the genetic alteration.

Monsanto sells, and allows other companies to sell, Roundup Ready soybean seeds to growers who assent to a special licensing agreement. That agreement permits a grower to plant the purchased seeds in one (and only one) season. He can then consume the resulting crop or sell it as a commodity, usually to a grain elevator or agricultural processor. But under the agreement, the farmer may not save any of the harvested soybeans for replanting, nor may he supply them to anyone else for that purpose. These restrictions reflect the ease of producing new generations of Roundup Ready seed. Because glyphosate resistance comes from the seed's genetic material, that trait is passed on from the planted seed to the harvested soybeans: Indeed, a single Roundup Ready seed can grow a plant containing dozens of genetically identical beans, each of which, if replanted, can grow another such plant – and so on and so on. The agreement's terms prevent the farmer from co-opting that process to produce his own Roundup Ready seeds, forcing him instead to buy from Monsanto each season.

Petitioner Vernon Bowman is a farmer in Indiana who, it is fair to say, appreciates Roundup Ready soybean seed. He purchased Roundup Ready each year, from a company affiliated with Monsanto, for his first crop of the season. In accord with the agreement just described, he used all of that seed for planting, and sold his entire crop to a grain elevator (which typically would resell it to an agricultural processor for human or animal consumption).

Bowman, however, devised a less orthodox approach for his second crop of each season. Because he thought such late-season planting "risky," he did not want to pay the premium price that Monsanto charges for Roundup Ready seed. He therefore went to a grain elevator; purchased "commodity soybeans" intended for human or animal consumption; and planted them in his fields. Those soybeans came from prior harvests of other local farmers. And because most of those farmers also used Roundup Ready seed, Bowman could anticipate that many of the purchased soybeans would contain Monsanto's patented technology. When he applied a glyphosate-based herbicide to his fields, he confirmed that this was so; a significant proportion of the new plants survived the treatment, and produced in their turn a new crop of soybeans with the Roundup Ready trait. Bowman saved seed from that crop to use in his late-season planting the next year – and then the next, and the next, until he had harvested eight crops in that way. Each year, that is, he planted saved seed from the year before (sometimes adding more soybeans bought from the grain elevator), sprayed his fields with glyphosate to kill weeds (and any non-resistant plants), and produced a new crop of glyphosate-resistant –

i.e., Roundup Ready – soybeans.

After discovering this practice, Monsanto sued Bowman for infringing its patents on Roundup Ready seed. Bowman raised patent exhaustion as a defense, arguing that Monsanto could not control his use of the soybeans because they were the subject of a prior authorized sale (from local farmers to the grain elevator). The District Court rejected that argument, and awarded damages to Monsanto of $84,456.

II

The doctrine of patent exhaustion limits a patentee's right to control what others can do with an article embodying or containing an invention. Under the doctrine, the initial authorized sale of a patented item terminates all patent rights to that item. And by exhaust[ing] the [patentee's] monopoly" in that item, the sale confers on the purchaser, or any subsequent owner, the right to use [or] sell" the thing as he sees fit. **??**. We have explained the basis for the doctrine as follows: "[T]he purpose of the patent law is fulfilled with respect to any particular article when the patentee has received his reward ... by the sale of the article"; once that "purpose is realized the patent law affords no basis for restraining the use and enjoyment of the thing sold." *Id*.

Consistent with that rationale, the doctrine restricts a patentee's rights only as to the "particular article" sold; it leaves untouched the patentee's ability to prevent a buyer from making new copies of the patented item. The purchaser of the patented machine does not acquire any right to construct another machine either for his own use or to be vended to another. Rather, a second creation of the patented item calls the monopoly, conferred by the patent grant, into play for a second time. That is because the patent holder has "received his reward" only for the actual article sold, and not for subsequent recreations of it. If the purchaser of that article could make and sell endless copies, the patent would effectively protect the invention for just a single sale. Bowman himself disputes none of this analysis as a general matter: He forthrightly acknowledges the "well settled" principle "that the exhaustion doctrine does not extend to the right to 'make' a new product."

Unfortunately for Bowman, that principle decides this case against him. Under the patent exhaustion doctrine, Bowman could resell the patented soybeans he purchased from the grain elevator; so too he could consume the beans himself or feed them to his animals. Monsanto, although the patent holder, would have no business interfering in those uses of Roundup Ready beans. But the exhaustion doctrine does not enable Bowman to make additional patented soybeans without Monsanto's permission (either express or implied).

And that is precisely what Bowman did. He took the soybeans he purchased home; planted them in his fields at the time he thought best; applied glyphosate to kill weeds (as well as any soy plants lacking the Roundup Ready trait); and finally harvested more (many more) beans than he started with. That is how "to 'make' a new product," to use Bowman's words, when the original product is a seed. Because Bowman thus reproduced Monsanto's patented invention, the exhaustion doctrine does not protect him.

Were the matter otherwise, Monsanto's patent would provide scant benefit. After inventing the Roundup Ready trait, Monsanto would, to be sure, receive its reward for the first seeds it sells. But in short order, other seed companies could reproduce the product and market it to growers, thus depriving Monsanto of its monopoly. And farmers themselves need only buy the seed once, whether from Monsanto, a competitor, or (as here) a grain elevator. The grower could multiply his initial purchase, and then multiply that new creation, ad infinitum – each time profiting from the patented seed without compensating its inventor. Bowman's late-season plantings offer a prime illustration. After buying beans for a single harvest, Bowman saved enough seed each year to reduce or eliminate the need for additional purchases. Monsanto still held its patent, but received no gain from Bowman's annual production and sale of Roundup Ready soybeans. The exhaustion doctrine is limited to the "particular item" sold to avoid just such a mismatch between invention and reward.

Bowman principally argues that exhaustion should apply here because seeds are meant to be planted. The exhaustion doctrine, he reminds us, typically prevents a patentee from controlling the use of a patented product following an authorized sale. And in planting Roundup Ready seeds, Bowman continues, he is merely using them in the normal way farmers do. Bowman thus concludes that allowing Monsanto to interfere with that use would "creat[e] an impermissible exception to the exhaustion doctrine" for patented seeds and other "self-replicating technologies.

But it is really Bowman who is asking for an unprecedented exception – to what he concedes is the "well settled" rule that "the exhaustion doctrine does not extend to the right to 'make' a new product." Reproducing a patented article no doubt "uses" it after a fashion. But as already explained, we have always drawn the boundaries of the exhaustion doctrine to exclude that activity, so that the patentee retains an undiminished right to prohibit others from making the thing his patent protects. See, e.g., *Cotton–Tie Co. v. Simmons* (holding that a purchaser could not "use" the buckle from a patented cotton-bale tie to "make" a new tie). That is because, once again, if simple copying were a protected use, a patent would plummet in value after the first sale of the first item containing the invention. The undiluted patent

Cotton-Tie: 106 U.S. 89 (1882)

monopoly, it might be said, would extend not for 20 years (as the Patent Act promises), but for only one transaction. And that would result in less incentive for innovation than Congress wanted. Hence our repeated insistence that exhaustion applies only to the particular item sold, and not to reproductions.

Nor do we think that rule will prevent farmers from making appropriate use of the Roundup Ready seed they buy. Bowman himself stands in a peculiarly poor position to assert such a claim. As noted earlier, the commodity soybeans he purchased were intended not for planting, but for consumption. Indeed, Bowman conceded in deposition testimony that he knew of no other farmer who employed beans bought from a grain elevator to grow a new crop. So a non-replicating use of the commodity beans at issue here was not just available, but standard fare. And in the more ordinary case, when a farmer purchases Roundup Ready seed qua seed – that is, seed intended to grow a crop – he will be able to plant it. Monsanto, to be sure, conditions the farmer's ability to reproduce Roundup Ready; but it does not – could not realistically – preclude all planting. No sane farmer, after all, would buy the product without some ability to grow soybeans from it. And so Monsanto, predictably enough, sells Roundup Ready seed to farmers with a license to use it to make a crop. Applying our usual rule in this context therefore will allow farmers to benefit from Roundup Ready, even as it rewards Monsanto for its innovation.

Still, Bowman has another seeds-are-special argument: that soybeans naturally "self-replicate or 'sprout' unless stored in a controlled manner," and thus "it was the planted soybean, not Bowman" himself, that made replicas of Monsanto's patented invention. But we think that blame-the-bean defense tough to credit. Bowman was not a passive observer of his soybeans' multiplication; or put another way, the seeds he purchased (miraculous though they might be in other respects) did not spontaneously create eight successive soybean crops. As we have explained, Bowman devised and executed a novel way to harvest crops from Roundup Ready seeds without paying the usual premium. He purchased beans from a grain elevator anticipating that many would be Roundup Ready; applied a glyphosate-based herbicide in a way that culled any plants without the patented trait; and saved beans from the rest for the next season. He then planted those Roundup Ready beans at a chosen time; tended and treated them, including by exploiting their patented glyphosate-resistance; and harvested many more seeds, which he either marketed or saved to begin the next cycle. In all this, the bean surely figured. But it was Bowman, and not the bean, who controlled the reproduction (unto the eighth generation) of Monsanto's patented invention.

Our holding today is limited – addressing the situation before us, rather than every one involving a self-replicating product. We rec-

ognize that such inventions are becoming ever more prevalent, complex, and diverse. In another case, the article's self-replication might occur outside the purchaser's control. Or it might be a necessary but incidental step in using the item for another purpose. *Cf.* 17 U.S.C. § 117(a)(1) ("[I]t is not [a copyright] infringement for the owner of a copy of a computer program to make ... another copy or adaptation of that computer program provide[d] that such a new copy or adaptation is created as an essential step in the utilization of the computer program"). We need not address here whether or how the doctrine of patent exhaustion would apply in such circumstances. In the case at hand, Bowman planted Monsanto's patented soybeans solely to make and market replicas of them, thus depriving the company of the reward patent law provides for the sale of each article. Patent exhaustion provides no haven for that conduct.

In the Canandian case of *Monsanto Canada Inc. v. Schmeiser*, 2001 FCT 256, a farmer argued that Roundup Ready seeds had blown onto his fields, or been carried by insects. But the court did not have to consider the legal consequences of these possibilities, because "none of the suggested sources could reasonably explain the concentration or extent of Roundup Ready canola of a commercial quality evident from the results of tests on Schmeiser's crop."

With respect to a medical practitioner's performance of a medical activity that constitutes an infringement under section 271(a) or (b), the provisions of sections 281, 283, 284, and 285 [i.e., all meaningful remdedies] shall not apply against the medical practitioner or against a related health care entity with respect to such medical activity.

§ 287(c)(1)
Limitation on damages and other remedies; marking and notice

Why are doctors special?

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. There's a quick hit on biologics a little further down.

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)

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.

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

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

Now twenty years.

35 U.S.C. § 154.

35 U.S.C. § 271(a)

at once. Thus, if the discovery relates to a product that cannot be marketed without substantial testing and regulatory approval, the "clock" on his patent term will be running even though he is not yet able to derive any profit from the invention.

The second distortion occurred at the other end of the patent term. In 1984, the Court of Appeals for the Federal Circuit decided that the manufacture, use, or sale of a patented invention during the term of the patent constituted an act of infringement, see § 271(a), even if it was for the sole purpose of conducting tests and developing information necessary to apply for regulatory approval. *See 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.

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

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:

Informally known as Hatch-Waxman, after its Congressional champions

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."

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.

35 U.S.C. § 271(e)(1)

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. They failed, and (*Generix*) explains why. So the baseline remained that a generic drug requires a full NDA of its own.

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

1. It gives generic firms the option of filing an "abbreviated" NDA, or ANDA, in place of a full NDA based on new clinical trials (*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

[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.

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 testing process, after which, if successful, the manufacturer will receive marketing approval from the FDA. *See* 21 U.S.C. § 355(b)(1) (requiring, among other things, "full reports of investigations" into safety and effectiveness; "a full list of the articles used as components"; and a "full description" of how the drug is manufactured, processed, and packed).

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

21 U.S.C § 355(j)(5)(f)(ii)

> 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 …

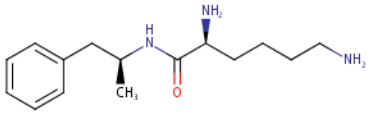
21 U.S.C. § 355(j)(5)(F)(iii)

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.

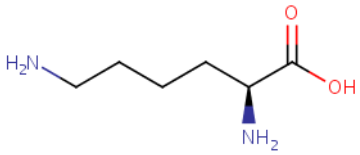
21 C.F.R. § 314.108(a) & (b)(2))

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 conducted 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."]



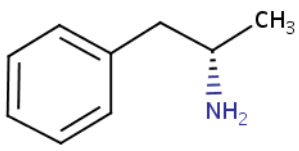
Lisdexamfetamine



Lysine

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 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.



Dextroamphetamine

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.

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

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.

Drug approval isn't the only case of data exclusivity in federal law. For example, the Federal Insecticide, Fungicide, and Rodenticide Act, which is understandably concerned with the safety of chemicals being used for their toxic qualities, has its own data exclusivity regime administered by the EPA.

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.

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

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 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 de-

pends 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 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.

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

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

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 ap-

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

proved; or (bb) an approved method of using the drug."

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

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."

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

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 antitrust 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

21 U.S.C § 355(j)(5)(B)(iv)

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.

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 antitrust 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 … un-

21 U.S.C. § 360cc(a)

> til the expiration of seven years from the date of approval of the approved application. …

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 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-

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

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.