A Review of Recent U.S. Pharmaceutical and Biotechnology Patent Cases

March 18, 2016

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1. A claimed antiviral drug was held to be obvious, despite the antiviral drug being a new chemical entity.

2. A once-monthly oral dosing regimen was found to be obvious despite evidence that it had higher efficacy compared to prior art dosage regimens.

3. Pharma patent was unenforceable due to inequitable conduct before the USPTO.

4. A district court's ruling of non-enablement was overturned because the defendant provided no evidence of undue experimentation.

5. A biosimilar lawsuit was dismissed for lack of standing since the biosimilar product was in a clinical trial.

6. Disputes prior to issuance of a patent were held to be justiciable controversies as the basis for a declaratory judgment lawsuit.

7. The Federal Circuit did not find any clear error in the district court's conclusion that the infringer failed to prove by clear and convincing evidence that a food effect for the micronized formulation was known in the art, but found an error in the district court's reliance on the doctrine of inherency to disclose the food effect limitation.

8. A primer was held to be ineligible matter for patent based on the Supreme Court's holding in *Myriad*. Claims of the patent that require comparing a patient's gene with the wild-type and identifying any differences are patent ineligible subject matter in view of *Alice*.

9. Patent claims were held to be nonobvious because the prior art failed to meet the claimed strength, dissolution limitations, and claimed amounts of modified release polymers.

10. Claims to a diagnostic test using cell-free fetal DNA (cffDNA) were held to be not patent eligible under 35 U.S.C. § 101.

11. Patent claims directed to sequencing deoxyribonucleic acid (DNA) are invalid as obvious.

12. A subsection (k) applicant (biosimilar) may only give effective notice of commercial marketing after the FDA has licensed its product, effectively delaying launch of a biosimilar product by six months.

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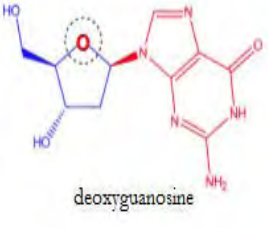
1. *Bristol-Myers Squibb Co. v. Teva Pharmaceuticals USA, Inc.*, 769 F.3d 1339 (Fed. Cir. 2014).

The Federal Circuit affirmed the district court's ruling that the claimed antiviral drug was obvious, despite the antiviral drug being a new chemical entity.

Bristol-Myers Squibb (BMS) modified the natural nucleoside 2′-deoxyguanosine (deoxyguanosine), which resulted in the product Entecavir. The product is structurally identical to deoxyguanosine except for one difference: it has a carbon-carbon double bond (also known as an exocyclic methylene group) at the 5′ position of the carbocyclic ring, while deoxyguanosine has an oxygen atom.

Claimed Compound	Prior Art Lead Compound
 entecavir	 deoxyguanosine

The district court held that one of ordinary skill in the art would have been motivated to select 2′-CDG as a lead compound and to modify it to obtain the claimed compound. Expert testimony revealed that in choosing whether to modify 2′-CDG's carbocyclic ring or its guanine base, the carbocyclic portion of 2′-CDG would be retained. However, testimony also showed that other chemists were making changes to the carbocyclic portion. Teva's expert also testified that changing the carbocyclic portion resulted in greater activity than changes to the guanine ring. Accordingly, this was a natural decision because the goal was to develop antivirals with improved activity. Unrefuted expert testimony also explained how the next obvious choice for modification would have been either the 2′ or 5′ position on the

carbocyclic ring, because those were the only two locations where small changes could easily be made to the molecule. A skilled artisan would focus on the smallest elements on the top row of the periodic table, including carbon and fluorine. In addition to expert testimony, the court stated that toxicity concerns did not prevent BMS from using 2'-CDG as a starting point.

Although BMS argued that a new chemical entity, as a matter of law, cannot be obvious when the claimed invention possesses unexpected properties, the Federal Circuit explained that an unexpected result or property does not by itself support a finding of nonobviousness.

2. *Hoffmann-La Roche Inc. v. Apotex Inc., 748 F. 3d 1326 (Fed. Cir. 2014).*

A once-monthly oral dosing regimen was found to be obvious despite evidence that it had higher efficacy compared to prior art dosages.

The issue in this case is whether it would have been obvious at the time of invention to select a once-monthly oral dosing regimen of ibandronate to treat osteoporosis and to set that dose at 150 mg, as claimed in the asserted patent. A representative claim on appeal reads as follows:

> 1. A method for treating or inhibiting postmenopausal osteoporosis in a postmenopausal woman in need of treatment or inhibition of postmenopausal osteoporosis by administration of a pharmaceutically acceptable salt of ibandronic acid, comprising:
>
> (a) commencing the administration of the pharmaceutically acceptable salt of ibandronic acid by orally administering to the postmenopausal woman, on a single day, a first dose in the form of a tablet, wherein the tablet comprises an amount of the pharmaceutically acceptable salt of ibandronic acid that is equivalent to about 150 mg of ibandronic acid; and
>
> (b) continuing the administration by orally administering, once monthly on a single day, a tablet comprising an amount of the pharmaceutically acceptable salt of ibandronic acid that is equivalent to about 150 mg of ibandronic acid.

With regard to monthly dosing, prior art disclosed a preferred embodiment in which "a dosage form of the invention is administered to a patient . . . preferably once a month." With respect to the selection of a specific 150 mg monthly dose, the Federal Circuit relied on a prior art reference that disclosed 2.5 and 5 mg daily doses "showed positive outcome in all regions." Additionally, another prior art reference disclosed weekly doses of ibandronate "from the group

consisting of 35 mg, 40 mg, 45 mg, or 50 mg." The 35 mg weekly dose of ibandronate is equivalent to a 5 mg daily dose, which appears in the aforementioned prior art references. This suggested that there was a reasonable expectation of success with the total-dose equivalents of the 5 mg daily dose. Based on the daily and weekly dosage disclosed in the prior art, the Federal Circuit held that it would be obvious to extrapolate a monthly dose of 150 mg (5 mg/day x 30 days = 150 mg/month).

The Federal Circuit found the claim obvious despite conceding that the 150 mg resulted in greater efficacy:

> "While the evidence would support a finding of superior efficacy of the 150 mg monthly dose in raising BMD levels, as compared to a 2.5 mg daily dose, that improved efficacy does not rebut the strong showing that the prior art disclosed monthly dosing and that there was a reason to set that dose at 150 mg. . . . The evidence of superior efficacy does nothing to undercut the showing that there was a reasonable expectation of success with the 150 mg monthly dose, even if the level of success may have turned out to be somewhat greater than would have been expected. For the same reasons, the nonlinear bioavailability of ibandronate does not rebut the prima facie showing of obviousness of a once monthly dose of 150 mg."

The dissent believed the claim to be nonobvious because the once-a-month dose approach "required twelve years of research and clinical testing and evaluation to demonstrate its efficacy when dosed once a month and its safety at this high monthly dosage." Without the "extensive exploration," the successful method of a monthly dose would not have been successful. Furthermore, prior art does not show or suggest the single dose of 150 mg in addition to once-a-month administration. The dissent also expressed concern over the court's ruling, stating that improvements will be discouraged, and relied on the following data which illustrates the 150mg dose resulting in unexpectedly high amount of ibandronate in serum.

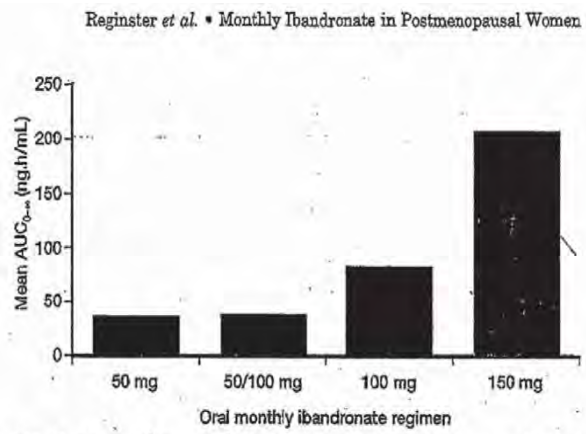


FIG. 3. Mean $AUC_{0-\infty}$ for monthly oral ibandronate in serum (initial dose only).

3. *Apotex Inc. v. UCB, Inc., 763 F.3d 1354 (Fed. Cir. 2014).*

The Federal Circuit affirmed the district court holding that U.S. Patent No. 6,767,556 (the '556 patent) was unenforceable due to inequitable conduct before the USPTO.

The '556 patent is directed to the manufacture of moexipril tablets.

Moexipril is an angiotension-converting ("ACE") inhibitor and is susceptible to degradation and instability. Claim 1, the only independent claim which relates to the improved stability of the compound, reads as follows:

> 1. A process of making a solid pharmaceutical composition comprising moexipril magnesium, said process comprising the step of reacting moexipril or an acid addition salt thereof with an alkaline magnesium compound in a controlled manner in the presence of a sufficient amount of solvent for a predetermined amount of time so as to convert greater than 80% of the moexipril or moexipril acid addition salt to moexipril magnesium.

The explanation for need of a solvent as noted in claim 1 is known as "wet granulation" and has been known in the industry since the 1980s. To overcome a prior art reference, U.S. Patent No. 4,743,450 (the '450 patent), the patentee argued that its product contained moexipril hydrochloride and magnesium oxide is therefore "capable of an acid-base reaction that is difficult to control and results in uncertainty regarding the final composition of the product." The patentee further submitted an expert declaration which stated that the alkaline magnesium compound in the prior art '450 patent behaved as a stabilizer and did not react. The declaration further stated that a person of ordinary skill in the art would not expect a reaction to occur between the moexipril and the alkaline stabilizer. The patentee then amended the claim to state at least an 80% conversion, as opposed to the claimed "greater than 80%," to distinguish the prior art in which there was no reaction.

Prior to a jury trial for the infringement of the '556 patent, a bench trial was held pertaining to claim construction and equitable defenses. The district court held that the patentee committed inequitable conduct during prosecution because the patentee was aware of a reaction in the prior art between the moexipril and the alkaline magnesium compound. The inventor conceded during trial that he had a "strong suspicion" and a "belief" that the prior art was made according to his claimed process. Additionally, the inventor conducted tests that compared the prior art to a moexipril product with no alkaline stabilizer. In his handwritten notes, the inventor concluded that the Apotex product was "much less stable than the magnesium salt," which implied at least a suspicion that the prior art consisted of moexipril magnesium. Approximately one month later, the inventor's suspicion was confirmed by two Apotex scientists who produced a detailed mass spectrometry report on the prior art and concluded that moexipril in the prior art is "mainly present" as moexipril magnesium. Based on these facts, the Federal Circuit affirmed the district dourt's finding of inequitable conduct.

4. *Alcon Research Ltd. v. Barr Laboratories, Inc., 745 F. 3d 1180 (Fed. Cir. 2014).*

The Federal Circuit overturned the district court's ruling of non-enablement because the defendant provided no evidence of undue experimentation.

The claim at issue pertains to the addition of an amount of polyethoxylated castor oil (PECO) to enhance the stability of a composition comprising prostaglandin:

> 1. A method of enhancing the chemical stability of an aqueous composition comprising a therapeutically-effective amount of a prostaglandin, wherein the method comprises adding a chemically stabilizing amount of a polyethoxylated castor oil [("PECO")] to the composition.

The district court found that the claim was not enabled because of many "variables," including the number of prostaglandins and the range of PECOs encompassed by the claims. Additionally, the claim was not enabled because there were "[v]arious parameters including pH, buffer, buffer concentration, preservatives, chelating agents, and other excipients which may affect the chemical stability of prostaglandins in ophthalmic formulations."

The Federal Circuit reversed the district court's finding of non-enablement, stating that the defendant's evidence that addressed non-enablement was based on unsubstantiated conclusory statements, "which was not sufficient."

> Barr adduced no evidence at trial that changing any of the "variables" or "[v]arious parameters" identified by the district court would render Alcon's claimed invention inoperable, nor was there any evidence that experimenting with those variables was required for an ordinarily skilled artisan to be capable of increasing the chemical stability of a prostaglandin by adding PECO. Adjusting variables may be relevant to optimizing the stability of a given prostaglandin composition, but Barr proffered no evidence that any experimentation, let alone undue experimentation, with those variables would be necessary in order to practice the claimed invention. Without that evidence, there is no foundation for the district court's nonenablement ruling.

The Federal Circuit also held that the particular claims of the patent were enabling, based on the disclosure of exemplary formulations, various classes of prostaglandins, various types of PECOs, and stability data. The district court's nonenablement ruling was reversed.

5. *Sandoz Inc. v. Amgen Inc., 773 F.3d 1274 (Fed. Cir. 2014).*

The Federal Circuit affirmed dismissal of a declaratory judgment claim because plaintiff had no standing to

initiate a biosimilar lawsuit since the biosimilar product was in a clinical trial.

Sandoz sought declaratory judgment, arguing that that use of the biological product would not constitute infringement of any valid claim of two Amgen patents because both patents were "unenforceable due to prosecution laches, and . . . both patents [were] invalid." Although Sandoz conducted Phase III clinical trials of the drug product in dispute, it had not filed an application with the Food and Drug Administration (FDA). In response to the declaratory judgment, Amgen moved for complaint dismissal arguing that the court did not have jurisdiction due to a lack of "real and immediate injury or threat of future injury" caused by Amgen. The district court dismissed the infringement case:

> "Any dispute about patent infringement is at present subject to significant uncertainties--concerning whether it will actually arise and if so, what specific issues will require decision. Sandoz's Phase III trial may fail in material ways. If so, perhaps Sandoz will not file for approval, thereby eliminating altogether the patent dispute it has asked the district court to adjudicate. Perhaps, if the trial materially fails, i.e., uncovers significant problems, Sandoz will instead modify its proposed product and ultimately file for FDA approval of the modified product. At a minimum, that scenario could alter the content of any patent dispute: notably, infringement of the specific claims of the specific patents . . .could present different questions depending on the precise product."

Sandoz did not show an immediate harm from the inability to seek or secure patent adjudication prior to filling an application for FDA approval. Because Sandoz did not meet the Article III requirements of immediacy and reality, the district court's declaratory judgment dismissal was affirmed.

6. *Danisco 2 US Inc. v. Novozymes A/S, 744 F.3d 1325 (Fed. Cir. 2014).*

The Federal Circuit held that disputes prior to issuance of a patent can be the basis of a justiciable controversy for a declaratory judgment.

Danisco U.S. Patent No. 8,084,240 (the '240 patent) issued on December 27, 2011, claiming priority from a June 6, 2009 provisional application. The active ingredient is a claimed α-amylase variant polypeptide enzyme with a substitution from glutamic acid to proline. After receiving its Notice of Allowance, Novozymes amended a pending application (later issued as U.S. Patent No. 8,252,573, [the '573 patent]) to claim Danisco's claimed enzyme with the same substitution.

After Novozymes's '573 patent was issued, Danisco sought declaratory judgment. In response, Novozymes moved for complaint dismissal and

claimed lack of jurisdiction, which was granted. The court reasoned that a justiciable controversy did not exist because Danisco challenged Novozymes's '573 patent the day that it was issued. Therefore, Novozymes could not have taken any affirmative action to enforce its patent rights. Although there was prior litigation history between the two parties, the district court held that the history did not support a conclusion that an actual controversy existed. The district court ruled that the presence of "pre-issuance conduct" between the parties was not enough to constitute an affirmative act. The Federal Circuit dismissed the district court's reasoning, stating that "[t]he district court's categorical distinction between pre- and post-issuance conduct is . . . irreconcilable with the Supreme Court's insistence on applying a flexible totality of the circumstances test, its rejection of technical bright line rules in the context of justiciability, and our own precedent."

The pre-issuance activity in this case which demonstrated that the two parties have "been at war" over patent involving the claimed enzyme included:

> Novozymes's sole enzyme claimed in its '573 patent was the same claim as Danisco's '240 patent; the record indicates that Novozymes sought its patent due to the belief that Danisco would infringe once their claim issued; Novozymes asserted on two occasions that Danisco's '240 patent was invalid and should not be entitled to a patent on the claimed enzyme; Novozymes sued Danisco or its predecessors twice for infringement of related liquefaction products.

The Federal Circuit held that Novozymes's activities demonstrate a "preparedness and a willingness to enforce its patent rights," which is enough to support a conclusion that subject matter jurisdiction existed. The totality of the circumstances in the instant case established a justiciable controversy and the dismissal of Danisco's complaint for subject matter jurisdiction was reversed and remanded for further proceedings.

7. *Par Pharmaceutical, Inc. v. TWi Pharmaceuticals, Inc., 773 F.3d 1186 (Fed. Cir. 2014).*

The Federal Circuit did not find any clear error in the district court's conclusion that the infringer failed to prove by clear and convincing evidence that a food effect for the micronized formulation was known in the art, but found an error in the district court's reliance on the doctrine of inherency to disclose the food effect limitation.

The patent claimed a method of using a nanosized megestrol formulation to "increase the body mass in a human suffering from . . . loss of body mass." Par Pharmaceuticals (Par) was approved to market the generic version of micronized megestrol, and through reformulation, reduced the

particle size to the nanometer range. Although the nanosized formulation showed a reduced food effect, the U.S. Patent and Trademark Office (USPTO) rejected Par's method of using the nanosized formulation as obvious in light of the micronized prior art formulation. Subsequent to the rejection, Par amended its independent claims by adding two "wherein" clauses that addressed food effect limitations as follows:

> ". . . wherein after a single administration in a human subject of the formulation there is no substantial difference in the Cmax of megestrol when the formulation is administered to the subject in a fed versus a fasted state,
>
> wherein fasted state is defined as the subject having no food within at least the previous 10 hours, and wherein fed state is defined as the subject having a high-calorie meal within approximately 30 minutes of dosing."

The USPTO granted the patent with the above amended claims and the Food and Drug Administration (FDA) approved the nanoparticle formulation.

TWi Pharmaceuticals (TWi) filed an ANDA and sought approval to market a generic form of Par's nanosized formula and Par filed suit claiming infringement. TWi stated that Par's claims were obvious under 35 U.S.C. § 103, did not contain patentable subject matter under § 101, and were not enabling under § 112.

The Federal Circuit did not find any clear error in the district court's conclusion that the infringer failed to prove by clear and convincing evidence that a food effect for the micronized formulation was known in the art. The Federal Circuit did, however, find error in the district court's reliance on the doctrine of inherency to disclose the food effect limitation. Inherent teachings are a question of fact and in order to rely on inherency, the limitation at issue "necessarily must be present, or [must be] the natural result of the combination of elements explicitly disclosed by the prior art." Because there were no findings of fact regarding these limitations, the Federal Circuit vacated the district court's inherency analysis and remanded to determine if TWi presented evidence that the claimed food effect is necessarily present in the prior art combination.

The district court also found motivation to combine prior art referenced, and the Federal Circuit agreed. Par argued that there was no motivation to combine because a person of ordinary skill in the art at the time of the invention "would not have been motivated to combine nanoparticle technology with micronized megestrol to abrogate a food effect." Because the food effect was unknown at the time of invention, it is unclear how the inventors were motivated to nanosize the formulation. The Federal Circuit found that the district court's examination of alternate motivations was not done in error. The alternate motivation

analyzed by the district court was the viscosity of the micronized formulation. Due to its highly viscous properties, AIDS patients had difficulty swallowing the micronized formulation. Because it was known in the art that NanoCrystal technology could reduce viscosity, one in ordinary skill in the art would know that reduced particle size could lead to improved bioavailability. Therefore, motivation to create a nanosized formulation was present and the district court did not err in their conclusion that motivation to combine megestrol with nanoparticle technology was present.

Additionally, the district court held that there was a likelihood of success in combining megestrol with nanoparticle technology. The court held that a person of ordinary skill in the art would believe making nanoparticles was not difficult, could be successfully implemented, and could reduce viscosity. Prior art disclosed that the use of nanoparticle technology had evolved to be reliable and showed consistency regarding properties such as viscosity.

While the Federal Circuit agreed with the district court's conclusions regarding motivation to combine references, expectations of success from combining, and that the '576 patent was nonobvious, the district court's judgment was vacated and remanded for further analysis regarding the inherency on the food effect limitation.

8. *In re BRCA1- & BRCA2-Based Hereditary Cancer Test Patent Litigation, 774 F.3d 755 (Fed. Cir. 2014).*

A primer, which is a strand of short nucleic acid sequences that serves as a starting point for DNA synthesis, held to be patent ineligible matter based on the Supreme Court's holding in *Myriad*. The Federal Circuit also applied the Supreme Court's decision in *Alice* to invalidate two claims of the patent that require comparing a patient's gene with the wild-type and identifying any differences.

The issue in this case was whether a primer, which is a strand of short nucleic acid sequences that serves as a starting point for DNA synthesis, is patent ineligible matter based on the Supreme Court's holding in *Myriad.* (*In Association for Molecular Pathology v. Myriad*, 133 S. Ct. 2107 (2013)), the Supreme Court held that isolated DNA claims were patent ineligible because the location and order of the nucleotides existed in nature before Myriad found them." and ''Myriad's principal contribution was uncovering the precise location and genetic sequence of the BRCA[genes]." However, in Myriad the Supreme Court found the cDNA claims to be patent eligible under § 101because cDNA is an exon-only sequence, with no introns, that does not occur in nature.

The Federal Circuit held that primers are not distinguishable from the isolated DNA found patent-ineligible in Myriad and are not similar to the cDNA found to be patent-eligible. Primers necessarily contain the

identical sequence of the gene sequence directly opposite to the strand to which they are designed to bind. They are structurally identical to the ends of DNA strands found in nature, and are patent ineligible. The Federal Circuit also dismissed the notion that primers are in fact not naturally occurring because single-stranded DNA cannot be found in the human body, noting that the Supreme Court made clear, "separating [DNA] from its surrounding genetic material is not an act of invention." See *Alice Corp. v. CLS Bank Int'l*, 134 S. Ct. 2347 (2014) ("*Alice*").

The Federal Circuit also applied the Supreme Court's decision in *Alice* to invalidate two claims of the patent that require comparing a patient's gene with the wild-type and identifying any differences. In *Alice*, the Supreme Court reiterated its two-step test to determine patent eligibility for any claims that allegedly encompass abstract ideas. First, "we determine whether the claims at issue are directed to [a] patent-ineligible concept[ ]. If so, we then ask, 'what else is there in the claims before us?' Based on the test set out in *Alice*, the comparisons described in the claims are directed to the patent-ineligible abstract idea of comparing BRCA sequences and determining the existence of alterations. The methods, directed to identification of alterations of the gene, require merely comparing the patient's gene with the wild-type and identifying any differences that arise. The claim thus recites nothing more than the abstract mental steps necessary to compare two different nucleotide sequences: one looks at the first position in a first sequence; determines the nucleotide sequence at that first position; looks at the first position in a second sequence; determines the nucleotide sequence at that first position; determines if the nucleotide at the first position in the first sequence and the first position in the second sequence are the same or different, wherein the latter indicates an alteration; and repeats the process for the next position. Having determined that the comparison steps of the method claims are abstract ideas, the Federal Circuit moves to the second step of Alice and considered whether the particular mechanism for the comparisons added by claims renders the claims patent-eligible. The Federal Circuit then held that set forth well-understood, routine and conventional activity engaged in by scientists at the time of Myriad's patent application.

The district court's denial of Myriad's injunctive relief was affirmed.

9. *Ferring B.V. v. Watson Laboratories, Inc., 764 F.3d 1401 (Fed. Cir. 2014).*

The Federal Circuit affirmed the district court ruling that the patent claims are not obvious for failing to meet the claimed strength, dissolution limitations, and claimed amounts of modified release polymers.

Ferring B.V. (Ferring) owns U.S. Patent Nos. 7,947,739 (the '739 patent), 8,022,106 (the '106 patent), and 8.273.795 (the '795 patent), which are

modified release formulations of tranexamic acid under the brand name Lysteda® for the treatment of heavy menstrual bleeding known as menorrhagia. The patent claims have three essential elements, one of which requires about 650 mg of tranexamic acid. Almost one year prior to Ferring's patents issued, Watson filed an ANDA and sought the FDA's approval to market generic versions of Lysteda®.

The court held that prior art did not set forth limitations nor provide reason to motivate the combination of teachings to "derive the claimed formulation with specific dissolution profiles." Watson contended that each of Ferring's claim limitations were disclosed or suggested in prior art. To support this contention, Watson presented a 2007 report that evaluated the safety and efficacy of a 500 mg tranexamic acid product. According to Watson, it would have been obvious to increase the dosage to 650 mg and to modify the drug in packaging suitable for oral dosage. Although Ferring argued that prior art taught away from using a dosage as high as 650 mg, the court agreed with Watson for the following four reasons:

1. Prior art references disclose 500 mg tranexamic acid formulations without indicating higher tablet strengths. The report upon which Watson relies specifically notes that an increased dose of tranexamic acid results in increased in gastrointestinal side effects.
2. The references do not disclose the claimed amounts of modified release polymers. While the report does list species of excipients, there is no specified amount present in the formulation of the polymer or any other active ingredient.
3. Watson did not identify any prior art references that disclose the critical dissolution limitations of the patented claims. Rather, Watson merely asserted in a conclusory manner that those limitations would have been obvious and failed to address why one of ordinary skill in the art would choose the specific release profiles claimed.
4. Supporting evidence demonstrated that there was a long-felt and unmet need for a treatment for menorrhagia that avoided adverse events. This was demonstrated by the FDA's "fast track" status grant to Ferring in order to expedite product review of Lysteda®.

The district court holding that Watson did not provide clear and convincing evidence that Ferring's patents were invalid as obvious under § 103 was affirmed.

10. *Ariosa Diagnostics, Inc. v. Sequenom, Inc. 788 F. 3d 1371 (Fed. Cir. 2015).*

Claims to a diagnostic test using cell-free fetal DNA (cffDNA) were held to be not patent eligible under 35 U.S.C. § 101.

U.S. Patent No. 6,258,540 (the '540 patent) is owned by Sequenom and claims methods of using cell-free fetal DNA (cffDNA), a non-cellular fetal DNA that circulates freely in the blood stream of a pregnant woman. The use of cffDNA could be used to detect the "small fraction of paternally inherited cffDNA in maternal plasma or serum to determine fetal characteristics, such as gender." Appellee Ariosa Diagnostics Inc. (Ariosa) makes and sells another non-invasive test used to determine prenatal diagnosis of fetal characteristics. Ariosa and its licensee sought declaratory judgment after receiving infringement threats on behalf of Sequenom, who then filed a counterclaim of infringement of the '540 patent. Both Ariosa and Sequenom filed cross motions for summary judgment regarding invalidity under 35 U.S.C § 101.

The district court held that the claims of the '540 patent did not add enough to the natural phenomenon of paternally inherited cffDNA to make the claims patentable under § 101. The '540 patent merely applied "well-understood, routine processes to paternally inherited cffDNA, a natural phenomenon." Additionally, the district court found that the claimed process "posed a risk of preempting a natural phenomenon." To determine whether the exception is applicable, the court first addressed whether the concept was patent ineligible. Because the method begins and ends with the taking and location nucleic acids within cffDNA, the claims related to matter that occurs naturally therefore rendering the concept patent ineligible The court then moved to the second prong of the test and considered whether the additional elements of each claim transformed the nature of the claim into a patent-eligible application. The court found that method steps of the preparation and amplification of DNA sequences in plasma or serum were well-understood, conventional and routine as stated in the specification, and therefore not new and useful.

Although Sequenom argued that there are other uses for cffDNA aside from uses claimed in the '540 patent and that the application of the natural phenomenon embodied narrow and specific claims, the court held that "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."

The district court's summary judgment ruling was affirmed.

11. *Trustees of Columbia Univ. v. Illumina, Inc., Case No. 2014-1547, 2015 U.S. App. LEXIS 12343 (Fed. Cir. July 17, 2015)*

The Federal Circuit affirmed the Patent Trial and Appeal Board (PTAB) decision that patents directed to sequencing deoxyribonucleic acid (DNA) are invalid as obvious.

DNA is composed of double-stranded molecules called nucleotides, and each nucleotide consists of three distinct parts: a sugar, a base, and one or more phosphate groups. Frederick Sanger and Alan Coulson invented a sequencing method that relied on dideoxynucleotides (ddNTPs), which have a hydrogen atom (H) rather than OH at the 3′ position. An electrophoresis step caused Sanger's sequencing to be to slow in order to effectively sequence entire genomes. Thereafter, a new type of process called sequencing by synthesis (SBS) avoided the need for electrophoresis by placing removable "caps" at the 3′-OH group. However, this process interfered with its operation because the "caps" were located in close proximity to the active site of the polymerase. According to Columbia University, Dr. Jingyue Ju and his colleagues avoided this problem by placing an unlabeled removable cap on the 3′-OH group and attaching the label to a cleavable linker attached to deazapurine base.

Columbia University asserted that it would not be obvious at the time of invention to use a "reversible chain-terminating nucleotide with a label attached to the base, rather than to the cap on the 3′-OH group of the sugar." While Columbia University conceded there was interest in the lease-labeled nucleotide analogues, it argued that the most relevant reference, Tsien, contained a preference of labeling the 3′-OH caps rather than the base. However, Tsien noted that the label could be attached to the base, noting that it should not be implied that the base is the only place where labeling can occur. Therefore, the PTAB concluded that Columbia understated the interest level of base-labeled nucleotide analogues within the prior art. The PTAB also noted to other references that recognized base-labeled nucleotides containing removable 3′-OH moieties to be useful and effective methods.

Regarding motivation to combine, Columbia University argued that the PTAB "never identified any affirmative motivation that would have led a skilled artisan to abandon the 'ideal,' natural C-8 possession taught by Tsien." Although this position was ideal, the court had previously explained that better alternatives described in prior art does not mean that "an inferior combination is an apt for obviousness purposes."

With respect to the reasonable expectation of success, Illumina argued that a person having ordinary skill in the art could have reasonably expected that the combination of available references to synthesize a 3′-OH-capped nucleotide with a label attached to a deazapurine base would be successful. The court held that other patent disclosures were substantial evidence to support the PTAB's finding that there was a reasonable expectation of success in achieving the claimed invention.

While both parties presented arguments with respect to secondary considerations, the court held that they did not weigh strongly in favor of nonobviousness.

12. *Amgen Inc. v. Sandoz, Inc., 794 F.3d 1347 (Fed. Cir. 2015).*

A subsection (k) applicant (biosimilar) may only give effective notice of commercial marketing after the FDA has licensed its product, effectively delaying launch of a biosimilar product by six months.

Traditionally, and applicant who files a biologics license application (BLA) will provide clinical data to demonstrate product safety and efficacy. As an alternative, applicants may file an abbreviated biologics license application (aBLA) pursuant to 42 U.S.C. § 262(k) by submitting information to demonstrate that the product is "biosimilar" or "interchangeable" with a previously approved reference product. Additionally, the applicant may submit public information regarding the safety and effectiveness of the reference product.

Since 1991, Amgen marketed Neupogen® (filgrastim), and in May 2014, Sandoz sought FDA approval of a biosimilar filgrastim product and filed an aBLA. On July 8, 2014, Sandoz notified Amgen of the filing and its intention to launch the product upon FDA approval. Traditionally, the Food and Drug Administration (FDA) approves biological products by granting a license under 42 U.S.C. § 262(a). Amgen sued Sandoz, and amongst other matters, alleged that the Biologics Price Competition and Innovation Act of 2009 (BPCIA) was violated when Sandoz did not disclose required information and by giving a "premature, ineffective, notice of commercial marketing prior to FDA approval of the biosimilar product. The district court held that subsection (k) allows an applicant not to satisfy the obligation to give notice of commercial marketing under § 262(l)(8)(A) prior to FDA approval.

According to paragraph (l)(8)(A), "the subsection (k) applicant shall provide notice to the reference product sponsor not later than 180 days before the date of the first commercial marketing of the biological product license under subsection (k)." Amgen argued that the statute's purpose of providing time to seek preliminary injunction and resolve patent disputes is not satisfied when notice is provided after FDA licensure. The court agreed with Amgen, stating that a subsection (k) applicant may only give effective notice of commercial marketing after the FDA has licensed its product. Although a licensed product may be marketed, it does not necessarily follow that "whenever the future commercial marketing of a yet-to-be licensed product is discussed, it is the 'licensed' product." The court believed that Congress intended notice to follow licensing because it is after licensing that therapeutic uses and manufacturing processes are fixed. Once the scope of the approved license is known and marketing of the biosimilar product is determined, the reference product sponsor (RPS) may effectively choose whether to seek a preliminary injunction from the court.