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NONOBVIOUSNESS STANDARD FOR PROMOTING ONGOING DRUG DISCOVERY: A LESSON FROM *SANOFI-AVENTIS U.S., LLC V. DR. REDDY'S LABORATORIES, INC.*

PING-HSUN CHEN

ABSTRACT

This article explores *Sanofi-Aventis U.S., LLC v. Dr. Reddy's Laboratories, Inc.*, 933 F.3d 1367, 1375 (Fed. Cir. 2019), and focuses on the issue of nonobviousness under 35 U.S.C. § 103. The Federal Circuit has developed the lead compound analysis for determining whether a pharmaceutical compound is obvious in view of a lead compound and other prior art references. The key question is whether an ordinary skilled chemist would have a motivation or reason to select a lead compound and modify it to arrive at the claim compound. The *Sanofi-Aventis* court further provided an evidentiary rule that the motivation or reason should be based on both the structural similarity of tested prior art compounds and the test results of these compounds. This article argues that the *Sanofi-Aventis* approach not only follows the Supreme Court's principles, but also is beneficial to ongoing drug development.

Keywords: Obviousness, lead compound, pharmaceutical compound, cabazitaxel, Jevtana

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I. INTRODUCTION

Paclitaxel, docetaxel, and cabazitaxel (shown in Figures 1(a), 2(a) & 2(b)) are three cancer drugs (antimicrotubule chemotherapy agents) of the taxane family.[1] In the 1960s, a research project funded by the National Cancer Institute ("NCI") first isolated paclitaxel (Taxol®) as a natural compound from the bark of the Pacific yew tree (*Taxus brevifolia*).[2] In the late 1970s, paclitaxel was identified as showing antitumor activity in the mouse melanoma B16 model.[3] However, it was not until 1994 that Bristol-Myers Squibb ("BMS") completed a semisynthetic process for manufacturing paclitaxel without killing endangered Pacific yew trees.[4] BMS' process utilized a precursor, 10-deacetyl-baccatin III (10-DAB shown in Figure 1(b)) extracted from the common yew tree (*Taxus baccata*).[5] Finally, the U.S. Food and Drug Administration ("FDA") approved Taxol® for treating ovarian cancer in 1992 and breast cancer in 1994.[6]

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[1] Boyang Sun, Robert M. Straubinger & Jonathan F. Lovell, *Current Taxane Formulations and Emerging Cabazitaxel Delivery Systems*, 11(10) NANO RESEARCH 5193, 5193 (2018); *see also* National Cancer Institute, NCI Dictionary of Cancer Terms-Antimicrotubule Agent, NCI.GOV, https://www.cancer.gov/publications/dictionaries/cancer-terms/def/antimicrotubule-agent (last visited Jan. 17, 2020) (A "antimicrotubule agent" is a "type of drug that blocks cell growth by stopping mitosis (cell division) [through interfering] with microtubules (cellular structures that help move chromosomes during mitosis).").

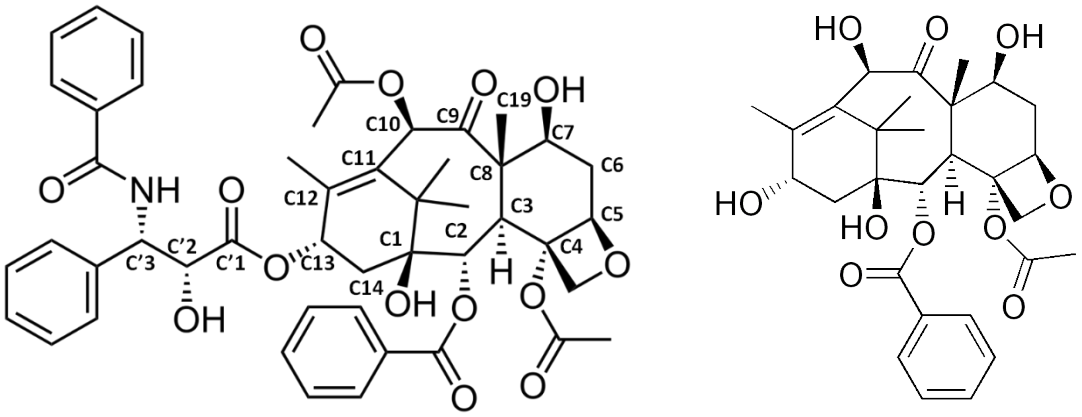
[2] NATIONAL CANCER INSTITUTE, SUCCESS STORY: TAXOL® (NSC 125973), https://dtp.cancer.gov/timeline/flash/success_stories/S2_Taxol.htm (last visited Jan. 16, 2020) [hereinafter NATIONAL CANCER INSTITUTE, TAXOL®]; *see* Matthieu Picard & Mariana C. Castells, *Re-visiting Hypersensitivity Reactions to Taxanes: A Comprehensive Review*, 49(2) CLINICAL REVIEWS IN ALLERGY & IMMUNOLOGY 177, 178 (2015).

[3] George Frisvold & Kelly Day-Rubenstein, *Bioprospecting and Biodiversity Conservation: What Happens When Discoveries Are Made?*, 50 ARIZ. L. REV. 545, 558-59 (2008) (describing the discovery and development of Taxol®); *see* NATIONAL CANCER INSTITUTE, TAXOL®, *supra* note 2; *see* Beth A. Weaver, *How Taxol/Paclitaxel Kills Cancer Cells*, 25 MOLECULAR BIOLOGY OF THE CELL 2677, 2677-78 (2014).

[4] Picard & Castells, *supra* note 2, at 178.

[5] *Id.*

[6] Weaver, *supra* note 3, at 2678 (Table 1).



(a) Paclitaxel (b) 10-Deacetylbaccatin III

Figure 1

Docetaxel (Taxotère®) was developed as a substitute to paclitaxel by Rhone-Poulenc Rorer ("RPR") and Centre National de la Recherche Scientifique, France during the late 1980s and early 1990s.[7] Docetaxel was also semisynthesized by utilizing 10-DAB as a precursor.[8] Since the FDA approved Taxotère® for treating advanced breast cancer in 1996,[9] docetaxel has been proved to improve the survival rate of patients with metastatic breast cancer better than paclitaxel.[10]

Docetaxel and paclitaxel are structurally similar except that the benzamide functional group (Ph(C=O)NH- at C'3) and acetoxy ($CH_3C(=O)$-O- at C10) in paclitaxel (shown in Figure 1(a)) are replaced by the *tert*-butyl carbamate functional group (*t*-BuO(C=O)NH- at C'3) and hydroxyl group (HO- at C10) in docetaxel (shown in Figure 2(a)).[11] However, they are different in their molecular pharmacology, pharmacokinetics, and pharmacodynamic profiles.[12]

Cabazitaxel (Jevtana®, shown in Figure 2(b)) is the second generation of taxanes for treating cancer.[13] Around 1989, Sanofi-Aventis began to search for taxane

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[7] Eric K. Rowinsky, *The Development and Clinical Utility of the Taxane Class of Antimicrotubule Chemotherapy Agents*, 48 ANN. REV. OF MED. 353, 354 (1997); *see* N Katsumata, *Docetaxel: An Alternative Taxane in Ovarian Cancer*, 89 (Suppl. 3) BRITISH J. OF CANCER S9, S9-S10 (2003); *see also* Aventis Pharma S.A. v. Hospira, Inc., 743 F. Supp. 2d 305, 320 (D. Del. 2010) (describing the clinic test of Taxotere®); I Adachi, *A Late Phase II Study of RP56976 (Docetaxel) in Patients with Advanced or Recurrent Breast Cancer*, 73 BRITISH J. OF CANCER 210, 210 (1996).

[8] Rowinsky, *supra* note 7, at 354.

[9] Iwao Ojima, Scott D. Kuduk & Subrata Chakravarty, *Recent Advances in the Medicinal Chemistry of Taxoid Anticancer Agents*, 4 ADVANCES IN MED. CHEMISTRY 69, 71 (1999).

[10] T. Vu et al., *Survival Outcome and Cost-Effectiveness with Docetaxel and Paclitaxel in Patients with Metastatic Breast Cancer: A Population-Based Evaluation*, 19(3) ANNALS OF ONCOLOGY 461, 463-64 (2008).

[11] Ojima et al., *supra* note 9, at 71.

[12] Iain Brown, Jay N. Sangrithi-Wallace & Andrew C. Schofield, *Antimicrotubule Agents*, ANTICANCER THERAPEUTICS 79, 81 (2008).

[13] Sun et al., *supra* note 1, at 5193.

analogs to treat cancers.[14] Taking docetaxel and paclitaxel as reference compounds, Sanofi-Aventis ended up with finding cabazitaxel in 1994. [15] Cabazitaxel is structurally similar to docetaxel, but two methoxy (H_3CO-) groups of cabazitaxel substitute for hydroxyl groups at C7 and C10 positions of docetaxel, as shown in Figure 2.[16]

Cabazitaxel was selected after a preclinical screening process aiming at finding "a compound as potent as docetaxel in tumor models sensitive to docetaxel and more potent than docetaxel in tumors resistant to chemotherapy[.]"[17] The drug resistance to taxanes in tumor cells is mainly associated with increased expression of multidrug resistance ("MDR1") gene that encodes P-glycoprotein ("Pgp").[18] Pgp is a drug efflux pump that removes drug molecules from a tumor cell. [19] Pgp decreases the intracellular concentration of anticancer drugs in a tumor cell, which inhibits the therapeutic effect.[20]

On June 17, 2010, the FDA approved Jevtana® for a treatment in combination with prednisone for men with metastatic castration-resistant prostate cancer ("mCRPC") who had already received a docetaxel-containing regimen. [21] The "Approved Drug Products with Therapeutic Equivalence Evaluations" (a.k.a "Orange Book") lists three patents for Jevtana®: U.S. Patent Nos. 5,847,170 ('170 Patent), 7,241,907, and 8,927,592 ('592 Patent).[22]

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[14] Sanofi-Aventis U.S. LLC v. Fresenius Kabi USA, LLC, No. CV147869MASLHG, 2018 WL 9364037, at *4-*5 (D.N.J. Apr. 25, 2018).

[15] *Id.* at *4.

[16] Olga Azarenko et al., *Antiproliferative Mechanism of Action of the Novel Taxane Cabazitaxel as Compared with the Parent Compound Docetaxel in MCF7 Breast Cancer Cells*, 13(8) MOLECULAR CANCER THERAPEUTICS 2092, 2093 (2014).

[17] Hervé Bouchard et al., *Novel Taxanes: Cabazitaxel Case Study*, ANALOGUE-BASED DRUG DISCOVERY III 319, 324 (2013).

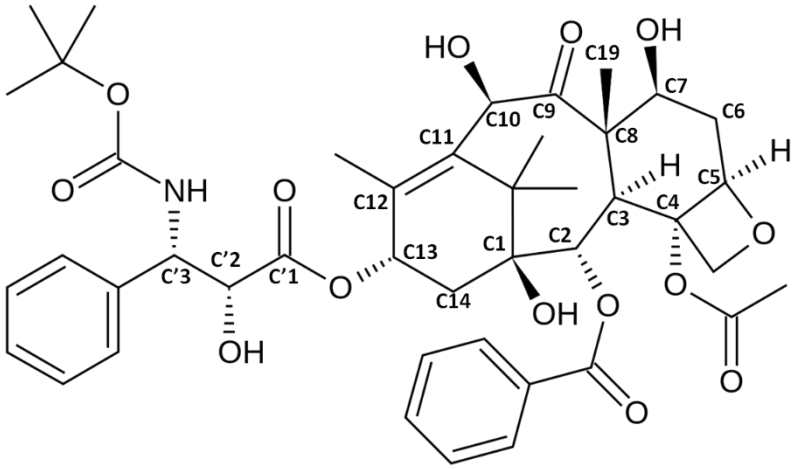
[18] Eugene Mechetner et al., *Levels of Multidrug Resistance (MDR1) P-glycoprotein Expression by Human Breast Cancer Correlate with In Vitro Resistance to Taxol and Doxorubicin*, 4 CLINICAL CANCER RESEARCH 389, 389 (1998); *see also* Afroz Abidi, *Cabazitaxel: A Novel Taxane for Metastatic Castration-Resistant Prostate Cancer-Current Implications and Future Prospects*, 4(4) J. OF PHARMACOLOGY AND PHARMACOTHERAPEUTICS 230, 232 (2013).

[19] Abidi, *supra* note 18, at 232.

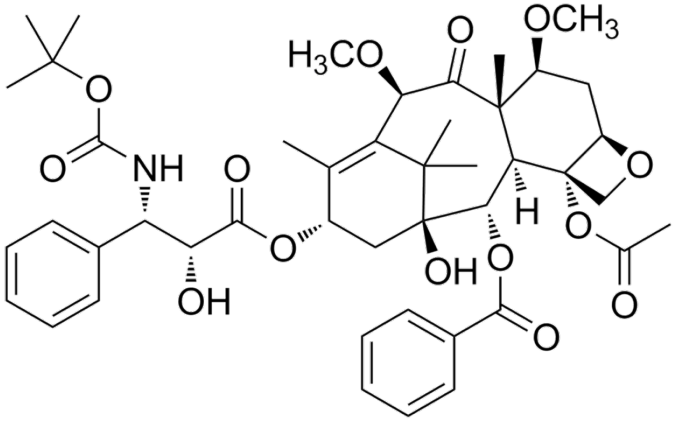
[20] Ziyad Binkhathlan & Afsaneh Lavasanifar, *P-glycoprotein Inhibition as a Therapeutic Approach for Overcoming Multidrug Resistance in Cancer: Current Status and Future Perspectives*, 13(3) CURRENT CANCER DRUG TARGETS 326, 329 (2013).

[21] Sanofi-Aventis U.S. LLC v. Fresenius Kabi USA, LLC, No. CV147869MASLHG, 2018 WL 9364037, at *3 (D.N.J. Apr. 25, 2018); *see* Ginah Nightingal & Jae Ryu, *Cabazitaxel (Jevtana)-A Novel Agent for Metastatic Castration-Resistant Prostate Cancer*, 37(8) PHARMACY AND THERAPEUTICS 440, 441 (2012).

[22] U.S. FOOD AND DRUG ADMINISTRATION [FDA], PATENT AND EXCLUSIVITY FOR: N201023, https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=201023&Appl_type=N (last visited Mar. 2, 2020).



(a) Docetaxel



(b) Cabazitaxel

Figure 2

The '170 Patent is entitled "Taxoids, Their Preparation and Pharmaceutical Compositions Containing Them."[23] Claim 1 recites "4α-Acetoxy-2α-benzoyloxy-5β,20-epoxy-1β-hydroxy-7β,10β-dimethoxy-9-oxo-11-taxen-13α-yl(2R,3S)-3-tert-butoxycarbonylamino-2-hydroxy-3-phenylpropionate," [24] which is the chemical formula of cabazitaxel.[25] Claim 2 recites "[a] pharmaceutical composition comprising at least the product according to claim 1 in combination with one or more

[23] *See Fresenius Kabi USA, LLC*, 2018 WL 9364037, at *2.

[24] Taxoids, Their Preparation and Pharmaceutical Compositions Containing Them, U.S. Patent No. 5,847,170 claim 1 (filed Mar. 26, 1996) (issued Dec. 8, 1998).

[25] *See* Crystalline Form of Cabazitaxel and Process for Preparing the Same, U.S. Patent No. 9,309,210 abstract (issued Apr. 12, 2016).

pharmaceutically acceptable diluents or adjuvants and optionally one or more compatible and pharmacologically active compounds."[26]

From 2014 to 2016, several generic drug companies filed an abbreviated new drug application ("ANDA") for Jevtana®.[27] The '170 Patent and '592 Patent were alleged to be invalid, which triggered multiple patent lawsuits brought by Sanofi-Aventis against these generic drug companies.[28] The lawsuits were consolidated in the United States District Court for the District of New Jersey.[29]

The defendants contended that claims 1 and 2 of the '170 Patent violated 35 U.S.C. § 103.[30] Section 103 requires that an invention may not be patented if the differences between the claimed invention and prior art are such that the claimed invention as a whole would have been obvious to a person having ordinary skill in the art before a specific date required by the patent law.[31] The key issue here was "whether a skilled artisan would have been motivated to replace the C7 and C10 hydroxyl groups of docetaxel with the methoxy groups of cabazitaxel."[32] Eventually, the district court found the disputed claims non-obvious in light of seven expert witnesses and seventeen prior art references.[33]

In 2019, the Federal Circuit in *Sanofi-Aventis U.S., LLC v. Dr. Reddy's Laboratories, Inc.* upheld the district court's nonobviousness decision.[34] This article attempts to demonstrate that the *Sanofi-Aventis* approach is an appropriate standard for the nonobviousness requirement of pharmaceutical compound patents, because the *Sanofi-Aventis* approach makes more likely patentable a pharmaceutical compound developed in the context of ongoing efforts among competing research groups.

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[26] '170 Patent, claim 2.

[27] *See Fresenius Kabi USA, LLC*, 2018 WL 9364037, at *3. The ANDA process can speed marketing of a generic version of a previously-approved new drug or pioneer drug without going through a full-scale clinic trial to show safety and effectiveness as the new drug had. *See* David C. McPhie, *Old Drugs, New Uses: Solving A Hatch-Waxman Patent Predicament*, 59 FOOD & DRUG L.J. 155, 158-59 (2004) (describing ANDA). Instead, showing that a generic version is bioequivalent to its pioneer counterpart is enough. The ANDA process requires a generic drug company to submit a Paragraph IV certificate if it wants the approval of its generic drug to be granted before the patents listed in the Orange Book for the pioneer drug expire. The process of filing a Paragraph IV certificate involves a patent dispute resolution mechanism. A generic drug company is obligated to challenge the validity of the relevant patents or assert non-infringement of these patents. To stop a generic version being marketed, a pioneer drug company has to sue the generic drug company for patent infringement under 35 U.S.C. § 271(e). *See* Quincy (Ping-Hsun) Chen, *Destroying A Pharmaceutical Patent for Saving Lives?: A Case Study of Sanofi-Synthelabo v. Apotex, Inc.*, 21 ALB. L.J. SCI. & TECH. 125, 133 (2011).

[28] Sanofi-Aventis U.S. LLC v. Fresenius Kabi USA, LLC, No. CV147869MASLHG, 2018 WL 9364037, at *1-*3 (D.N.J. Apr. 25, 2018).

[29] *Id.*

[30] *Id.* at *1, *3-*18, *37.

[31] *See* David Olson & Stefania Fusco, *Rules Versus Standards: Competing Notions of Inconsistency Robustness in Patent Law*, 64 ALA. L. REV. 647, 666-68, 666 n.91 (2013) (addressing the history of the Supreme Court's interpretation of 35 U.S.C. § 103).

[32] Sanofi-Aventis U.S., LLC v. Dr. Reddy's Labs., Inc., 933 F.3d 1367, 1375 (Fed. Cir. 2019).

[33] *See Fresenius Kabi USA, LLC*, 2018 WL 9364037, at *5-*11, *37.

[34] *See Sanofi-Aventis U.S., LLC*, 933 F.3d at 1370.

Next, Part II introduces the nonobviousness requirement imposed by the Supreme Court. Part III describes the evolution of the lead compound analysis specifically for determining whether a pharmaceutical compound patent is obvious. Part IV discusses the *Sanofi-Aventis* decision, including the technical background, key prior art references, Federal Circuit's reasoning, and implications drawn from the case. Last, Part V argues that the *Sanofi-Aventis* approach is beneficial to patenting activities of ongoing drug development among competing research groups.

II. 35 U.S.C. § 103, *GRAHAM* AND *KSR*

There are two important Supreme Court decisions defining the contour of the nonobviousness requirement.[35] In 1966, the Supreme Court in *Graham v. John Deere Company* instructed lower courts to evaluate four factors to determine whether a claim is obvious: (1) "the scope and content of the prior art"; (2) "differences between the prior art and the claims at issue"; (4) "the level of ordinary skill in the pertinent art"; and (4) "secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc."[36]

In 2007, the Supreme Court in *KSR International Co. v. Teleflex Inc.*[37] examined the Federal Circuit's teaching/suggestion/motivation ("TSM") test for the nonobviousness requirement.[38] Under the TSM test, "a patent claim is only proved obvious if 'some motivation or suggestion to combine the prior art teachings' can be found in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art.'"[39] However, the *KSR* Court criticized that the TSM test was too rigid to comply with its precedents.[40]

To reject the Federal Circuit's rigid approach, the *KSR* Court started with its precedents before and after 35 U.S.C. § 103 was enacted.[41] Eventually, the *KSR* Court laid down several principles for determining "whether a patent claiming the combination of elements of prior art is obvious."[42] First, "[w]hen a work is available in one field of endeavor, design incentives and other market forces can prompt

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[35] *See* Laura G. Pedraza-Fariña & Ryan Whalen, *A Network Theory of Patentability*, 87 U. CHI. L. REV. 63, 81-82 (2020) (analyzing Graham v. John Deere Co. of Kansas City, 383 U.S. 1 (1966), and KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398 (2007)).

[36] Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17-18 (1966); *see also* Insite Vision Inc. v. Sandoz, Inc., 783 F.3d 853, 858 (Fed. Cir. 2015) (quoting *Graham*, 383 U.S. at 17); *see also* Briana Barron, *Structural Uncertainty: Understanding the Federal Circuit's Lead Compound Analysis*, 16 MARQ. INTELL. PROP. L. REV. 401, 402 (2012) (discussing *Graham*).

[37] KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 398-428 (2007).

[38] *See* Mark D. Janis, *Tuning the Obviousness Inquiry After KSR*, 7 WASH. J.L. TECH. & ARTS 335, 342 (2012) (discussing the Federal Circuit's response to the Supreme Court's Decision in *KSR International Co.*).

[39] *KSR Int'l Co.*, 550 U.S. at 407.

[40] *Id.* at 419.

[41] *Id.* at 415-17.

[42] *KSR Int'l Co.*, 550 U.S. at 417; *see also* Katherine M. L. Hayes, *Three Years Post-KSR: A Practitioner's Guide to "Winning" Arguments on Obviousness and a Look at What May Lay Ahead*, 9 NW. J. TECH. & INTELL. PROP. 243, 246-48 (2010) (discussing five observations made by the KSR Court with regard to the obviousness analysis).

variations of it, either in the same field or a different one."[43] Therefore, if a predictable variation can be implemented by a person of ordinary skill, it is likely unpatentable under § 103.[44] Similarly, "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill."[45] The ultimate question is "whether the improvement is more than the predictable use of prior art elements according to their established functions."[46]

The *KSR* Court acknowledged that these principles may be more difficult to apply.[47] The *KSR* Court instructed that:

> a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was *an apparent reason to combine* the known elements in the fashion claimed by the patent at issue.[48]

In addition, the *KSR* Court required that the obviousness analysis "should be made explicit[,]" but courts "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ."[49]

Furthermore, the *KSR* Court clarified that in determining whether a claim is obvious, the objective reach of the claim matters, but the particular motivation or avowed purpose of the patentee doesn't.[50] Thus, a claim "can be proved obvious [] by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the claim]."[51]

From this aspect, the *KSR* Court offered additional principles.[52] First, "*any need or problem* known in the field of endeavor at the time of invention and *addressed by the patent* can provide a reason for combining the elements in the manner claimed."[53] Second, "[a] person of ordinary skill is also a person of ordinary creativity, not [the claimed technical solution]."[54] Third, "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options

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[43] KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 417 (2007).
[44] *Id.* at 417.
[45] *Id.*
[46] *Id.*
[47] *KSR Int'l Co.*, 550 U.S. at 417.
[48] *Id.* at 418 (emphasis added).
[49] *KSR Int'l Co.*, 550 U.S. at 417.
[50] *See id.* at 419.
[51] *Id.* at 419-20.
[52] *See id.* at 419-22.
[53] *KSR Int'l Co.*, 550 U.S. at 420 (emphasis added).
[54] *Id.* at 421.

within his or her technical grasp."[55] If the success of pursuing a known option would have been anticipated, "the fact that a combination was *obvious to try* might show that [the combination] was obvious under § 103."[56]

Finally, while cautioning that "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning[,]" the *KSR* Court rejected "[r]igid preventative rules that deny factfinders recourse to common sense" because such rules "are neither necessary under [its] case law nor consistent with it."[57]

III. LEAD COMPOUND ANALYSIS FOR PHARMACEUTICAL COMPOUND PATENTS

A. *Early Development*

The idea of "lead compound" in the context of analyzing the nonobviousness requirement of pharmaceutical compound claims first came to the Federal Circuit in *Yamanouchi Pharmaceutical Co., Ltd. v. Danbury Pharmacal, Inc.*[58] The patented compound there was famotidine used for inhibiting production of stomach acid to treat heartburn and ulcers.[59] The defendant alleged that two lead compounds would have been selected by one of skill in the art to form the claimed compound.[60]

Under four *Graham* factual factors,[61] the *Yamanouchi* court stated that "[f]or a chemical compound, a *prima facie* case of obviousness requires 'structural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions.'" [62] The court also required "a reasonable expectation of success, not absolute predictability" to support a conclusion of obviousness.[63] Ultimately, the court framed the obviousness issue as "whether one of skill in this art would have found motivation to combine pieces from one compound

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[55] *Id.* at 417.

[56] *Id.* (emphasis added).

[57] *Id.*

[58] Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc., 231 F.3d 1339, 1339-1348 (Fed. Cir. 2000); *see* Briana Barron, *Structural Uncertainty: Understanding the Federal Circuit's Lead Compound Analysis*, 16 MARQ. INTELL. PROP. L. REV. 401, 405 (2012) ("The earliest case establishing the modern 'lead compound' analysis is *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*").

[59] *Yamanouchi Pharm. Co.*, 231 F.3d at 1341.

[60] *Yamanouchi Pharm. Co.*, 231 F.3d at 1343-44; *see also* Appellants' Brief at 11-12, *Yamanouchi Pharm. Co.*, 231 F.3d 1339 (Fed. Cir. 2000) (Nos. 99-1521, 99-1522), 1999 WL 33631182 ("There is a common medicinal research technique known as 'lead-following'. When a particular new compound is known to be especially active for a particular intended use, a 'lead' compound, medicinal chemists modify the structure of the 'lead' compound slightly to produce another compound which is also expected to be active for the same use but is hoped to have improved pharmacological properties and fewer deficiencies.").

[61] *Yamanouchi Pharm. Co.*, 231 F.3d at 1343.

[62] *Id.* (quoting *In re* Dillon, 919 F.2d 688, 692 (Fed.Cir.1990) (en banc)).

[63] *See id.* (quoting *In re* Longi, 759 F.2d 887, 896 (Fed.Cir.1985)).

in a prior art patent with a piece of another compound in the second prior art patent through a series of manipulations."[64]

In *Eli Lilly and Co. v. Zenith Goldline Pharmaceuticals, Inc.*, the Federal Circuit again reviewed the defendant's argument that the district court clearly erred in requiring evidence of "a teaching or incentive to treat the closest prior art (i.e., Compound '222[, later known as ethyl olanzapine]) as a 'lead compound.'"[65] The patented compound was olanzapine used for treating schizophrenia.[66] The difference of olanzapine and Compound '222 was the ethyl substitution in Compound '222.[67]

The *Eli* court's nonobviousness analysis followed the "structural similarity" approach adopted the *Yamanouchi* court.[68] Further, the *Eli* court added two aspects that may negate obviousness.[69] First, "patentability for a chemical compound does not depend *only* on *structural similarity*."[70] Second, "[the] court will not ignore a *relevant property* of a compound in the obviousness calculus."[71] That is, "[w]hen claimed properties differ from the prior art, those differences, if unexpected and significant, may lead to nonobviousness."[72] Finally, the *Eli* court agreed with the district court's nonobviousness decision, because the evidence showed "the state of the art *would have directed* the person of ordinary skill in the art *away* from unfluorinated compounds like Compound '222."[73]

B. *Post-KSR Development*

Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd. was the Federal Circuit's first post-*KSR* decision where the defendant argued compound b would have been selected as a lead compound for making the patented compound, pioglitazone, used for treating Type 2 diabetes.[74]

The *Takeda* court held that *KSR International Co.* affirmed that the *Graham* factual factors still controls the nonobviousness analysis.[75] Under *KSR International Co.*, the *Takeda* court advanced the "structural similarity" approach in several aspects.[76] First, the court stated that "a prima facie case of obviousness also requires a showing of 'adequate support in the prior art' for *the change in structure*."[77]

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[64] *Yamanouchi Pharm. Co.*, 231 F.3d at 1343.

[65] Eli Lilly & Co. v. Zenith Goldline Pharm., Inc., 471 F.3d 1369, 1377 (Fed. Cir. 2006).

[66] *Id.* at 1373.

[67] *Id.* at 1375.

[68] *Id.* at 1377.

[69] *Id.* at 1378.

[70] *Eli Lilly & Co.*, 471 F.3d at 1378.

[71] *Eli Lilly & Co.*, 471 F.3d at 1377 (emphasis added).

[72] *Id.*

[73] *Id.* at 1379 (emphasis added).

[74] Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1352-54, 1356-57 (Fed. Cir. 2007); *see also* Dean L. Fanelli et. al., *2007 Patent Law Decisions of the Federal Circuit*, 57 AM. U. L. REV. 821, 926 (2008) (analyzing *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*).

[75] *See Takeda Chem. Indus., Ltd.*, 492 F.3d at 1355.

[76] *Id.* at 1356.

[77] *Id.* (emphasis added) (citing *In re* Grabiak, 769 F.2d 729, 731-32 (Fed. Cir.1985)).

Second, the *Takeda* court revisited its precedent and reaffirmed a precedential notion that "[n]ormally a prima facie case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound."[78] The court reasoned that "close or established '[s]tructural relationships may provide the requisite motivation or suggestion to modify *known compounds* to obtain new compounds.'"[79]

Third, the *Takeda* court stated that "[a] known compound may suggest its homolog, analog, or isomer[.]"[80] The court reasoned that "such compounds 'often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties.'"[81] In addition, the court emphasized that in such instances, "a showing that the 'prior art would have suggested making *the specific molecular modifications* necessary to achieve the claimed invention' was also required."[82]

Finally, the *Takeda* court concluded that under *KSR International Co.*, "in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to *modify a known compound in a particular manner* to establish prima facie obviousness of a new claimed compound."[83]

While the *Takeda* court focused on the finding of a "known compound," it learned from the defendant that a "lead compound" is "a compound in the prior art that would be most promising to modify in order to improve upon its antidiabetic activity and obtain a compound with better activity."[84] Eventually, the *Takeda* court upheld the district court's nonobviousness determination, because the defendant:

> failed to adduce evidence that compound b would have been selected as *the lead compound* and, even if that preliminary showing had been made, [the defendant] failed to show that there existed *a reason*, based on what was known at the time of the invention, to perform *the chemical modifications necessary* to achieve the claimed compounds.[85]

In *Eisai Co. v. Dr. Reddy's Laboratories, Ltd.*, the Federal Circuit recognized the "structural similarity" approach as "the analysis of the third *Graham* factor (the differences between the claimed invention and the prior art)" and stated that the analysis "often turns on the structural similarities and differences between the claimed compound and the prior art compounds."[86] In addition, while requiring

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[78] *Id.* (quoting *In re* Deuel, 51 F.3d 1552, 1558 (Fed.Cir.1995)) (alteration in original).

[79] *Id.* (quoting *Deuel*, 51 F.3d at 1558) (alteration in original and emphasis added).

[80] *Takeda Chem. Indus., Ltd.*, 492 F.3d at 1356.

[81] Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1355 (Fed. Cir. 2007) (quoting *Deuel*, 51 F.3d at 1558).

[82] *Id.* (quoting *Deuel*, 51 F.3d at 1558) (emphasis added).

[83] *Id.* at 1356-57 (emphasis added).

[84] *Id.* at 1357.

[85] *Takeda Chem. Indus., Ltd.*, 492 F.3d at 1362-63 (emphasis added).

[86] Eisai Co. v. Dr. Reddy's Labs., Ltd., 533 F.3d 1353, 1356-57 (Fed. Cir. 2008); *see also* Scott D. Locke & William D. Schmidt, *Protecting Pharmaceutical Inventions in A KSR World*, 50 IDEA 1, 16 (2009) (introducing Eisai Co. v. Dr. Reddy's Labs., Ltd., 533 F.3d 1353 (Fed. Cir. 2008)). *See Takeda Chem. Indus., Ltd.*, 492 F.3d at 1355 (the Federal Circuit discussed the "structural similarity" approach under the headline of "Differences Between the Prior Art and the Claims").

identification of a reason to modify a known compound, the *Eisai* court referred to "known compound" as "lead compound."[87]

Furthermore, the *Eisai* court reminded that under *KSR International Co.*, "the requisite motivation can come from any number of sources and need not necessarily be explicit in the art."[88] Thus, the court held that "it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship . . . to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old."[89]

Takeda Chemical Industries, Ltd. and *Eisai Co.* were later followed by *Altana Pharma AG v. Teva Pharmaceuticals USA, Inc.*[90] and *Daiichi Sankyo Co. v. Matrix Laboratories, Ltd.*[91] The *Daiichi* court further required the level of an ordinary skill in the art be a "medicinal chemist of ordinary skill" rather than a "chemist of ordinary skill."[92]

Finally, in *Unigene Laboratories, Inc. v. Apotex, Inc.*, the Federal Circuit further transformed the term "known compound" into "lead compound," when it developed a nonobviousness analysis for a drug formulation claim from the "structural similarity" approach.[93] The court stated that "[a] prima facie case of obviousness in the chemical arts is often based on a known compound, called a 'lead compound[.]'"[94] The court also defined a lead compound as something that "serves as a starting point for a person of ordinary skill developing the claimed invention" and "is often used to show structural similarities between the claimed compound and prior art."[95]

C. *Two-Part Inquiry: Otsuka Pharmaceutical Co. v. Sandoz, Inc.*

A line of cases after *Takeda Chemical Industries, Ltd.* shows that the Federal Circuit focused on whether a known or lead compound would have been modified to make the claimed compound, which is a single inquiry.[96] However, in 2012, the Federal Circuit in *Otsuka Pharmaceutical Co. v. Sandoz, Inc.* framed the lead compound analysis as a two-step analysis for the nonobviousness requirement of a new chemical compound.[97]

The *Otsuka Pharmaceutical Co.* court stated that "[o]ur case law demonstrates that whether a new chemical compound would have been prima facie obvious over

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[87] *See Eisai Co.*, 533 F.3d at 1357.

[88] *Id.* (citing Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293, 1301 (Fed. Cir. 2007)).

[89] *Id.* (quoting *Aventis Pharma Deutschland GmbH*, 499 F.3d at 1301).

[90] Altana Pharma AG v. Teva Pharm. USA, Inc., 566 F.3d 999, 1007 (Fed. Cir. 2009) (upholding the district court's denial of the plaintiff's motion for preliminary injunction).

[91] Daiichi Sankyo Co. v. Matrix Labs., Ltd., 619 F.3d 1346, 1352 (Fed. Cir. 2010).

[92] *Id*.

[93] Unigene Labs., Inc. v. Apotex, Inc., 655 F.3d 1352, 1361 (Fed. Cir. 2011).

[94] *Id.* (citing *Eisai Co.*, 533 F.3d at 1357).

[95] *Id.* (citing *Eisai Co.*, 533 F.3d at 1357).

[96] *See supra* Part III.B.

[97] *See* Robert J. Smyth et. al., *2012 Patent Law Decisions of the Federal Circuit*, 62 AM. U. L. REV. 827, 859 (2013) (briefing Otsuka Pharm. Co. v. Sandoz, Inc., 678 F.3d 1280 (Fed. Cir. 2012)).

particular prior art compounds ordinarily follows *a two-part inquiry*."[98] The first question asks "whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts."[99] The second question is "whether the prior art would have supplied one of ordinary skill in the art with *a reason or motivation* to modify a lead compound to make the claimed compound with *a reasonable expectation of success*."[100]

Regarding step one, the *Otsuka Pharmaceutical Co.* court described the nature of a lead compound in two aspects.[101] First, a lead compound is "a compound in the prior art that would be most promising to modify in order to improve upon its . . . activity and obtain a compound with better activity."[102] Second, a lead compound is "a natural choice for further development efforts."[103]

In addition, the *Otsuka Pharmaceutical Co.* court stated that when the parties disputes "the notion that a chemist must select one or more lead compounds[,]" step one analysis "focuses on those proposed lead compounds that the alleged infringer has attempted to prove, by clear and convincing evidence, that the skilled artisan would have had a reason to select from the panoply of known compounds in the prior art."[104] From this aspect, the court emphasized that "the analysis is guided by evidence of the compound's pertinent properties [that] may include positive attributes such as activity and potency; adverse effects such as toxicity and other relevant characteristics in evidence."[105]

Furthermore, the *Otsuka Pharmaceutical Co.* court cautioned that "[a]bsent a reason or motivation based on such prior art evidence, mere structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection."[106] This caution may help avoid impermissible *ex post* reasoning.[107]

As for step two, the *Otsuka Pharmaceutical Co.* court stated that "the reason or motivation for modifying a lead compound may come from any number of sources and need not necessarily be explicit in the prior art."[108] In addition, the court offered two evidentiary aspects of finding a reason or motivation.[109] First, the court noted that "it is the possession of *promising useful properties* in a lead compound that motivates a chemist to make structurally similar compounds."[110] Thus, step two still considers

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[98] Otsuka Pharm. Co. v. Sandoz, Inc., 678 F.3d 1280, 1291 (Fed. Cir. 2012) (emphasis added).

[99] *Id.* (citing *Eisai Co.*, 533 F.3d at 1359).

[100] *Id.* at 1292 (emphasis added).

[101] *See id.* at 1291.

[102] *Id.* (quoting Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1357 (Fed. Cir. 2007)).

[103] *Otsuka Pharm. Co.*, 678 F.3d at 1291 (quoting Altana Pharma AG v. Teva Pharm. USA, Inc., 566 F.3d 999, 1008 (Fed. Cir. 2009)).

[104] *Id.* at 1292.

[105] *Id.* (international citations omitted).

[106] *Id.*

[107] *See id.*

[108] *Otsuka Pharm. Co.*, 678 F.3d at 1292.

[109] *Otsuka Pharm. Co.*, 678 F.3d at 1292-93.

[110] *Id.* at 1292-93 (emphasis added) (quoting Daiichi Sankyo Co. v. Matrix Labs., Ltd., 619 F.3d 1346, 1354 (Fed. Cir. 2010)).

the compound's pertinent properties.[111] Second, the court held that "it is sufficient to show that the claimed and prior art compounds possess a '*sufficiently close relationship* . . . to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old."[112]

D. *Post-Otsuka Development*

The two-part analysis under *Otsuka Pharmaceutical Co.* has not become a standard of the Federal Circuit,[113] except for *Pfizer Inc. v. Teva Pharmaceuticals USA, Inc.*[114] and, arguably, *Bristol-Myers Squibb Co. v. Teva Pharmaceuticals USA, Inc.*[115]

Those latter cases not following the two-part inquiry can be divided into two categories. The first category includes *In re Rosuvastatin Calcium Patent Litigation*,[116] where the district court's decision on the defendant's "lead compound" argument came before *Otsuka Pharmaceutical Co.*[117] Relying on the single inquiry under *Takeda Chemical Industries, Ltd.*, the Federal Circuit upheld the district court's finding that the asserted prior art compound would not have been selected as a lead compound or modified to make the patented compound.[118]

The second category includes *Millennium Pharmaceuticals, Inc. v. Sandoz Inc.*,[119] *Amerigen Pharmaceuticals Limited v. UCB Pharma GmBH*,[120] and *Sanofi-Aventis U.S., LLC v. Dr. Reddy's Laboratories, Inc.*,[121] where the issue on appeal focused on whether the selected lead compound would have been modified to make

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[111] *See id.* at 1292.

[112] *Id.* at 1293 (emphasis added) (quoting Aventis Pharma Deutschland GmbH v. Lupin, Ltd., 499 F.3d 1293, 1301 (Fed. Cir. 2007) (determining whether a claimed compound is obvious because it is a purified form of a prior-art mixture)).

[113] *See, e.g.*, In re Rosuvastatin Calcium Patent Litig., 703 F.3d 511, 511-529 (Fed. Cir. 2012); Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc., 752 F.3d 967, 967-979 (Fed. Cir. 2014); Millennium Pharm., Inc. v. Sandoz Inc., 862 F.3d 1356, 1356-1370 (Fed. Cir. 2017); Amerigen Pharm. Ltd. v. UCB Pharma GmBH, 913 F.3d 1076, 1076-1089 (Fed. Cir. 2019).

[114] *See* Pfizer Inc. v. Teva Pharm. USA, Inc., 555 F. App'x 961, 969-70 (Fed. Cir. 2014).

[115] *See* Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc., 752 F.3d 967, 972-76 (Fed. Cir. 2014) (without referring to the two-part inquiry, upholding the district court's finding that "a skilled artisan would have selected 2'-CDG as a lead compound and made the minor modification to arrive at entecavir."). *See* Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc., 923 F. Supp. 2d 602, 654 (D. Del. 2013) (district court's obviousness determination followed the two-part inquiry under *Otsuka Pharmaceutical Co*).

[116] In re Rosuvastatin Calcium Patent Litig., 703 F.3d 511, 511-529 (Fed. Cir. 2012).

[117] *See* In re Rosuvastatin Calcium Patent Litig., 719 F. Supp. 2d 388, 388, 405 (D. Del. 2010), as revised (July 1, 2010) ("According to Defendants, Compound lb does not need to be shown to be the only possible starting point or the 'lead compound' in the development of rosuvastatin, but rather, that Compound lb would have been an obvious and suitable starting point from which to begin the development of rosuvastatin."); *see also In re Rosuvastatin*, 703 F.3d. at 516.

[118] *See In re Rosuvastatin*, 703 F.3d. at 517-18 (citing Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1357 (Fed. Cir. 2007)).

[119] Millennium Pharm., Inc. v. Sandoz Inc., 862 F.3d 1356, 1356-1370 (Fed. Cir. 2017).

[120] Amerigen Pharm. Ltd. v. UCB Pharma GmBH, 913 F.3d 1076, 1076-1089 (Fed. Cir. 2019).

[121] Sanofi-Aventis U.S., LLC v. Dr. Reddy's Labs., Inc., 933 F.3d 1367, 1367-1380 (Fed. Cir. 2019).

the claimed compound.[122] But, the *Millennium* court followed *Otsuka Pharmaceutical Co.*,[123] while the *Amerigen* court and *Sanofi-Aventis* court followed *Takeda Chemical Industries, Ltd.*[124]

E. *Sanofi-Aventis U.S., LLC v. Dr. Reddy's Laboratories, Inc.*

In *Sanofi-Aventis U.S., LLC*, the district court impliedly applied the two-part inquiry by holding:

> [A] POSA [(person of ordinary skill in the art)] would have selected either docetaxel or paclitaxel as a lead compound, which does not foreclose Defendants' ease. Defendants, however, failed to demonstrate that a POSA would have been motivated to simultaneously modify docetaxel with a methyl ether at the [C7] and [C10] positions to arrive at cabazitaxel.[125]

On appeal, the Federal Circuit seemed to go back to the single inquiry under *Takeda Chemical Industries, Ltd.* by quoting: "[I]n cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."[126] Thus, it is sufficient to say that the uniform standard for the nonobviousness requirement of a pharmaceutical compound is not settled.

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[122] *See, e.g.*, *Millennium Pharm., Inc.*, 862 F.3d at 1364 ("The parties agree that bortezomib is the proper lead compound for this analysis."); *Amerigen Pharm. Ltd.*, 913 F.3d at 1080 ("In its obviousness analysis, the Board accepted that a person of ordinary skill would have chosen 5-HMT as a lead compound for development . . . . However . . . the Board found that a person of ordinary skill would not have been motivated to modify 5-HMT to make a prodrug[.]"); *see also Sanofi-Aventis U.S., LLC*, 933 F.3d at 1375 ("The court found that a person of ordinary skill would have selected docetaxel as a lead compound, and the key issue was thus whether a skilled artisan would have been motivated to replace the C7 and C10 hydroxyl groups of docetaxel with the methoxy groups of cabazitaxel.").

[123] *See Millennium Pharm., Inc.*, 862 F.3d at 1364 (quoting *Otsuka Pharm. Co.*, 678 F.3d at 1292).

[124] *See, e.g.*, *Amerigen Pharm. Ltd.*, 913 F.3d at 1089 (quoting *Takeda Chem. Indus., Ltd.*, 492 F.3d at 1356); *Sanofi-Aventis U.S., LLC*, 933 F.3d at 1375 (quoting *Takeda Chem. Indus., Ltd.*, 492 F.3d at 1357).

[125] Sanofi-Aventis U.S. LLC v. Fresenius Kabi USA, LLC, No. CV147869MASLHG, 2018 WL 9364037, at *11 (D.N.J. Apr. 25, 2018).

[126] *Sanofi-Aventis U.S., LLC*, 933 F.3d at 1375 (quoting *Takeda Chem. Indus., Ltd.*, 492 F.3d at 1357).

IV. ANALYSIS OF SANOFI-AVENTIS U.S., LLC V. DR. REDDY'S LABORATORIES, INC.

A. *Patented Technology*

Around 1989, Sanofi-Aventis' scientists used paclitaxel and docetaxel as reference compounds to develop taxane analogs that work as well as docetaxel in treating sensitive tumors and have better activity than docetaxel in confronting resistant tumors.[127] The desired taxane analogs were expected to be more soluble in water.[128]

The development involved modifications to the side chain at C13 position and the core at C2, C4, C5, C6, C7, C9 and C10 positions by adding different functional groups and changing the stereochemistry of different portions of, for example, docetaxel.[129] It took days or months to complete a successful synthesis of a certain compound.[130]

A newly-synthesized compound was examined by a series of *in vitro* and *in vivo* tests.[131] The first test was an *in vitro* tubulin polymerization assay for determining whether a compound acts as a taxane.[132] The second test was an *in vitro* cellular assay for assessing a compound's potency in sensitive and resistant tumor cell lines by comparing the performance of candidate compounds and docetaxel in each cell line.[133] The last test was an *in vivo* animal test for understanding the activity of a candidate compound in mice bearing tumors treated with docetaxel.[134] After the researchers, including the three inventors of the '170 Patent, reviewed the test data, they would decide which new compounds should move forward.[135]

Cabazitaxel was not a successful candidate in the beginning because of unsuccessful modifications to C7 and C10 positions in docetaxel.[136] Rather, larotaxel (shown in Figure 3(a)) was the first candidate for further development.[137] Larotaxel discovered in January 1994 was made by replacing the hydroxyl groups at C7 and C10 positions of docetaxel with a cyclopropane structure (shown in Figure 3(b)) at C7,

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[127] *See Fresenius Kabi USA, LLC*, 2018 WL 9364037, at *4.

[128] *See id.*

[129] *See id.*

[130] *See id.*

[131] *See id.* at *5.

[132] *See Fresenius Kabi USA, LLC*, 2018 WL 9364037, at *5; *see also* CYTOSKELETON, INC., TUBULIN POLYMERIZATION ASSAY KIT (CAT. # BK006P) 5-7, https://www.cytoskeleton.com/pdf-storage/datasheets/bk006p.pdf (last visited Apr. 3, 2020). A tubulin polymerization assay is based on a scientific observation that "light is scattered by microtubules to an extent that is proportional to the concentration of microtubule polymer." Because "[c]ompounds or proteins that interact with tubulin will often alter one or more of the characteristic phases of polymerization[,]"a light-scattering measurement of the concentration of microtubule polymer can indicate whether a compound may act as an anti-cancer agent.

[133] *See Fresenius Kabi USA, LLC*, 2018 WL 9364037, at *5; *see also* Bouchard, *supra* note 17, at 328-30.

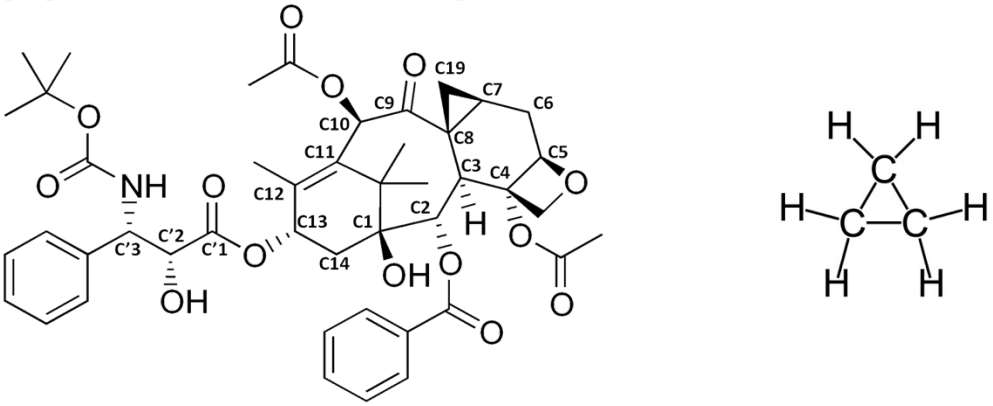
[134] *See Fresenius Kabi USA, LLC*, 2018 WL 9364037, at *5.

[135] *See id.*

[136] *See id.*

[137] *See id.*

C8, and C19 positions and an acetic acid functional group, respectively.[138] The cyclopropane structure resulted in better performance in those three tests.[139]



(a) Larotaxel (b) Cyclopropane

Figure 3

Before cabazitaxel was discovered, some docetaxel derivatives had been synthesized, for instance, one derivative with a methoxy group at C10 position and one derivative with an acetoxy group at C10 position.[140] However, the docetaxel derivative with a C10 acetoxy group was found to perform well in those *in vitro* or *in vivo* tests.[141] Eventually, on November 15, 1994, two methoxy groups were added onto C7 and C10 positions for the first time to complete the synthesis of cabazitaxel.[142] Among more than 450 compounds being synthesized and tested, only larotaxel and cabazitaxel entered into human studies.[143]

B. *Relevant Prior Arts*

The district court's nonobviousness decision was rested on seven witnesses and seventeen prior art references.[144] But, only nine references were introduced by the Federal Circuit.[145] They include:

(1) Hait's article[146]: Hait's research studied how phenothiazines (shown in Figure 4(a)) affect Pgp and showed that the increase of lipophilicity of phenothiazines

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[138] *See id.*; *see* Bouchard, *supra* note 17, at 325.

[139] *See Fresenius Kabi USA, LLC*, 2018 WL 9364037, at *5.

[140] *See id.*

[141] *See id.*

[142] *See id.*; *see* Bouchard, *supra* note 17, at 325-28.

[143] *See Fresenius Kabi USA, LLC*, 2018 WL 9364037, at *5.

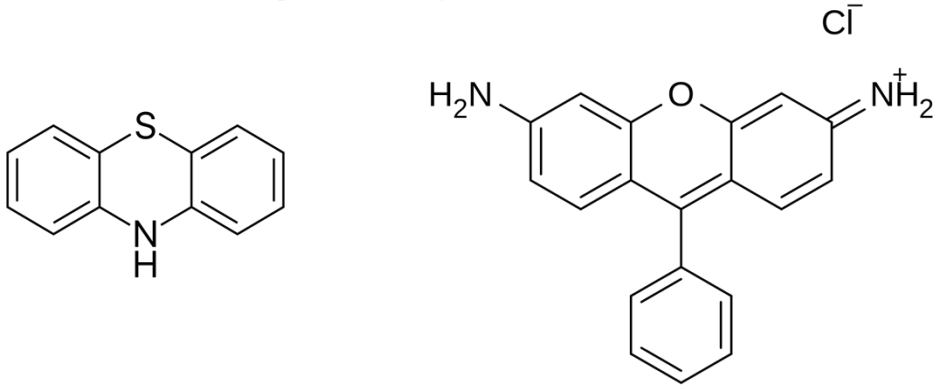
[144] *See* Sanofi-Aventis U.S., LLC v. Dr. Reddy's Labs., Inc., 933 F.3d 1367, 1375 (Fed. Cir. 2019).

[145] *See id.* at 1375-77.

[146] *See id.* at 1376 n.5 (citing William N. Hait & Dana T. Aftab, *Rational Design and Pre-Clinical Pharmacology of Drugs for Reversing Multidrug Resistance*, 43(1) BIOCHEMICAL PHARMACOLOGY 103, 103-07 (1992)); *see also Fresenius Kabi USA, LLC*, 2018 WL 9364037, at *9.

improves the sensitivity of a cancer cell line.[147] However, the district court found that phenothiazines were structurally quite different from taxanes and that nothing in Hait's article discussed the effect of taxanes on Pgp.[148] In addition, the district court found that Hait's research merely provided a hypothetical model of Pgp binding based on the binding phenomenon of a different protein.[149]

(2) Lampidis' article[150]: Lampidis' research indicated that the ability of positively-charged rhodamine dyes (shown in Figure 4(b)) to accumulate in, and eventually kill, drug-resistant cells gets better as their lipophilicity increases.[151] However, the district court found that Lampidis' article did not mention taxanes and that taxanes did not have a positive charge.[152]



(a) Phenothiazine (b) Rhodamine

Figure 4

(3) Commerçon's article[153]: Commerçon's article was written by scientists from RPR to report the impact on antimitotic activity caused by changes at certain positions on the taxane core.[154] Specifically, the article showed C'2, C'3, C7, C9 and C10 positions on paclitaxel could be modified.[155]

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[147] *See Sanofi-Aventis U.S., LLC*, 933 F.3d at 1376.

[148] *See id.*

[149] *See id.*

[150] *See id.* at 1376 n.6 (citing Theodore J. Lampidis et al., *Relevance of the Chemical Charge of Rhodamine Dyes to Multiple Drug Resistance*, 38(23) BIOCHEMICAL PHARMACOLOGY 4267, 4267-71 (1989)); *see also* Sanofi-Aventis U.S. LLC v. Fresenius Kabi USA, LLC, No. CV147869MASLHG, 2018 WL 9364037, at *10 (D.N.J. Apr. 25, 2018*).*

[151] *See Sanofi-Aventis U.S., LLC*, 933 F.3d at 1376; *see also Fresenius Kabi USA, LLC*, 2018 WL 9364037, at *10.

[152] *See Sanofi-Aventis U.S., LLC*, 933 F.3d at 1376.

[153] *See id.* at 1376 n.7 (citing A. Commerçon et al., *Practical Semisynthesis and Antimitotic Activity of Docetaxel and Side-Chain Analogues*, 583 TAXANE ANTICANCER AGENTS: BASIC SCIENCE AND CURRENT STATUS 233, 233-46 (G. I. Georg et al. eds., 1994)); *see also Fresenius Kabi USA, LLC*, 2018 WL 9364037, at *8.

[154] *See Fresenius Kabi USA, LLC*, 2018 WL 9364037, at *8.

[155] *See Sanofi-Aventis U.S., LLC*, 933 F.3d at 1376.

(4) Kingston's article[156]: Kingston's article provided what chemical modifications are tolerated at each position on taxane core.[157]

(5) Golik's patent[158]: Golik's European patent was filed by BMS.[159] Golik's patent disclosed some paclitaxel derivatives made by replacing the hydroxyl group at C7 position with a methylthiomethoxyl group (namely, 7-O-methylthiomethyl).[160] In an *in vitro* cellular test, one 7-O-methylthiomethyl paclitaxel derivative showed increased activity than paclitaxel and docetaxel.[161] However, the district court found that the modification of C7 position with a methylthiomethoxyl group could not lead to a methoxy substitution at the same position.[162]

(6) Ojima's article[163]: Ojima's article was co-authored by researchers from RPR.[164] The article taught that some substitutions at C'3 position produced much better activity than paclitaxel and docetaxel against a drug-resistant cell line.[165] Nothing about a methoxy substitution at C7 or C10 position was mentioned in the article.[166] Finally, the district court found that the article did not suggest increasing lipophilicity of C7 and C10 positions to against drug resistant cells.[167]

(7) Wong's patent[168]: Wong's U.S. patent was filed by BMS.[169] The patent disclosed a paclitaxel derivative with a methoxy at C7 position.[170] However, the district court found that the patent provided a more promising paclitaxel derivative with a modification at C'2 position and a different ether substitution at C7 position.[171] In addition, the court found that the patent did not disclose any compound with a hydroxy or methoxy at C10 position like docetaxel or cabazitaxel and any activity data from drug-resistant cell line tests.[172]

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[156] *See id.* at 1376 n.8 (citing David G. I. Kingston, *Recent Advances in the Chemistry and Structure-Activity Relationships of Paclitaxel*, 583 TAXANE ANTICANCER AGENTS: BASIC SCIENCE AND CURRENT STATUS 203, 203-216 (G. I. Georg et al. eds., 1994)); *see also Fresenius Kabi USA, LLC*, 2018 WL 9364037, at *9-*10.

[157] *See Fresenius Kabi USA, LLC*, 2018 WL 9364037, at *10.

[158] *See Sanofi-Aventis U.S., LLC*, 933 F.3d at 1376 (introducing European Patent No. 0,639,577); *see also Fresenius Kabi USA, LLC*, 2018 WL 9364037, at *8.

[159] *See Fresenius Kabi USA, LLC*, 2018 WL 9364037, at *8; *see also* European Patent No. 0,639,577 front page.

[160] *See Sanofi-Aventis U.S., LLC*, 933 F.3d at 1376; *see also* '577 European Patent ¶¶ 0011, 0194-0198.

[161] *See Sanofi-Aventis U.S., LLC*, 933 F.3d at 1376.

[162] *See id.* at 1376-77.

[163] *See id.* at 1377 n.9 (citing Iwao Ojima et al., *Syntheses and Structure-Activity Relationships of New Taxoids*, 583 TAXANE ANTICANCER AGENTS: BASIC SCIENCE AND CURRENT STATUS 262 (G. I. Georg et al. eds., 1994)); *see Fresenius Kabi USA, LLC*, 2018 WL 9364037, at *10.

[164] *See Fresenius Kabi USA, LLC*, 2018 WL 9364037, at *10.

[165] *See Sanofi-Aventis U.S., LLC*, 933 F.3d at 1377.

[166] *See id.*

[167] *See id.*

[168] *See id.* at 1377 (discussing U.S. Patent No. 6,201,140 (filed Mar. 13, 2001)); *see also Fresenius Kabi USA, LLC*, 2018 WL 9364037, at *11.

[169] *See* U.S. Patent No. 6,201,140 (filed Mar. 13, 2001).

[170] *See Sanofi-Aventis U.S., LLC*, 933 F.3d at 1377; *see also* '140 Patent col. 22 (examples 1 & 2), col. 23 (example 5).

[171] *See Sanofi-Aventis U.S., LLC*, 933 F.3d at 1377.

[172] *See id.*

(8) Kant's paper[173]: Kant's paper reported the results of taxane research at BMS.[174] The research focused on modifications at C10 position, including a methoxy substitution leading to a docetaxel-like compound with a methoxy at C10 position.[175] Modifications at C7 position were not studied.[176] All synthesized compounds were only tested with an *in vitro* tubulin polymerization assay.[177] However, the C10-methoxy docetaxel derivative was compared only to paclitaxel, not docetaxel.[178] The test result of the C10-methoxy docetaxel derivative was good, but another compound showed better performance.[179]

(9) Klein's paper[180]: The paper focused on modifications at C9 position and reported that some synthesized samples had better water solubility and stability than paclitaxel and showed excellent activity in an *in vitro* tubulin polymerization assay.[181] Among those synthesized compounds with better activity was a compound with a methoxy at C7 position.[182] However, the paper did not mention any modification at C10 position or any test data from tumor cell lines.[183]

Specifically, the Federal Circuit's nonobviousness holding was based on Hait's article, Lampidis' article, Commerçon's article, Ojima's article, and Golik's patent.[184]

C. *Federal Circuit's Reasoning*

On appeal, the appellant/defendant argued that the district court erred in rejecting its obviousness theory that "a skilled artisan would have: (1) been motivated to modify docetaxel to reduce Pgp-related drug resistance; (2) knew that this could be accomplished by increasing lipophilicity of the C7 and C10 positions; and (3) determined that methoxy substitutions were the 'smallest, most conservative' modification to achieve that goal."[185] But, the Federal Circuit sided with the appellee/patentee and held the argument was hindsight-driven.[186]

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[173] *See Sanofi-Aventis U.S., LLC*, 933 F.3d at 1377 n.10 (citing Joydeep Kant et al., *A Chemoselective Approach to Functionalize the C-10 Position of 10-Deacetylbaccatin III. Synthesis and Biological Properties of Novel C-10 Taxol® Analogues*, 35 TETRAHEDRON LETTERS 5543, 5543-46 (1994)); *see also* Sanofi-Aventis U.S. LLC v. Fresenius Kabi USA, LLC, No. CV147869MASLHG, 2018 WL 9364037, at *9 (D.N.J. Apr. 25, 2018).

[174] *See Fresenius Kabi USA, LLC*, 2018 WL 9364037, at *9.

[175] *See Sanofi-Aventis U.S., LLC*, 933 F.3d at 1377.

[176] *See id.*

[177] *See Fresenius Kabi USA, LLC*, 2018 WL 9364037, at *12; *see also Sanofi-Aventis U.S., LLC*, 933 F.3d at 1377.

[178] *See Sanofi-Aventis U.S., LLC*, 933 F.3d at 1377.

[179] *See id.*

[180] *See Sanofi-Aventis U.S., LLC*, 933 F.3d at 1377 n.11 (citing L. L. Klein et al., *Chemistry and Antitumor Activity in 9(R)-Dihydrotaxanes*, 583 TAXANE ANTICANCER AGENTS: BASIC SCIENCE AND CURRENT STATUS 276, 276-87 (G. I. Georg et al. eds., 1994)); *see also Fresenius Kabi USA, LLC*, 2018 WL 9364037, at *11.

[181] *See Sanofi-Aventis U.S., LLC*, 933 F.3d at 1377.

[182] *See id.*

[183] *See id.*

[184] *See id.* at 1378-80.

[185] *See id.* at 1378.

[186] *See Sanofi-Aventis U.S., LLC*, 933 F.3d at 1378.

First, the Federal Circuit agreed with the district court's finding that Hait's article and Lampidis' article "would not have provided a reason to make docetaxel more lipophilic [to combat drug resistance]."[187] The Federal Circuit found that both references did not study taxanes but compounds structurally different from taxanes.[188] The Federal Circuit also found that a hypothetical model in Hait's article was neither based on real Pgp nor cited by the prior art references discussing taxanes.[189]

Second, the Federal Circuit upheld the district court's finding of no motivation to make simultaneous methoxy substitutions at C7 and C10 positions to increase lipophilicity of docetaxel.[190] Although concluding that the prior art references showed substitutions at many positions on taxanes,[191] the Federal Circuit emphasized that no prior art reference actually "made simultaneous substitutions of any kind at C7 and C10 [positions]." [192] Additionally, in those references disclosing individual methoxy substitutions at C7 or C10 position, the Federal Circuit did not find any test result from drug-resistant cell lines or any indication that drug resistance can be overcome due to those methoxy substitutions.[193] Furthermore, the Federal Circuit criticized that the defendant mischaracterized or selectively read some prior art references to support its allegations.[194]

Third, the Federal Circuit rejected the defendant's view that simultaneous methoxy substitutions at C7 and C10 positions would have been made "because they are 'small, conservative changes' that increase lipophilicity."[195] The Federal Circuit specifically discussed the defendant's arguments based on Golik's patent and Ojima's article and concluded that these arguments were hindsight.[196]

Regarding Golik's patent, the defendant asserted that the teaching of C7 methylthiomethoxy substitutions would have supported a motivation to make a C7 methoxy substitution.[197] However, the Federal Circuit found no proof that a methoxy substitution would provide a similar benefit as a methylthiomethoxy substitution.[198] The Federal Circuit also criticized that the defendant's expert testimony on the properties of methylthiomethoxy was vague.[199]

As for Ojima's article, the defendant argued that the "implicit teaching of the benefits of a C10 *acetoxy* group against drug-resistant cells" would provide a motivation to make a methoxy substitution because methoxy "is smaller and more conservative."[200] However, the Federal Circuit found that the defendant failed to provide non-conclusory evidence or persuasive explanation to show that the methoxy

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[187] *Id*.
[188] *Id*.
[189] *Id*.
[190] *Id*.
[191] *See Sanofi-Aventis U.S., LLC*, 933 F.3d at 1378.
[192] *Id*.
[193] *Id*.
[194] *Id.* at 1378-79.
[195] *Id.* at 1379-80.
[196] *See Sanofi-Aventis U.S., LLC*, 933 F.3d at 1379-80.
[197] *Id.* at 1379.
[198] *Id*.
[199] *See id*.
[200] *See id*.

would be the same beneficial as the acetoxy or would serve a more conservative choice than the acetoxy.[201]

Lastly, the Federal Circuit responded to the defendant's challenge to the district court's decision on secondary considerations in favor of the patentee.[202] The Federal Circuit upheld the decision again, because the defendant failed to allege any error made by the district court.[203] Ultimately, the Federal Circuit held that the district court did not err in finding "[m]ultiple groups around the world tried unsuccessfully to develop taxanes into effective therapies and only [Sanofi] succeeded in developing a compound that showed superior activity over docetaxel, namely cabazitaxel, and obtained FDA approval."[204] Therefore, the Federal Circuit affirmed the district court's decision that claims 1 and 2 of the '170 Patent were not obvious in view of those prior art references.[205]

D. *Implication I: Motivation Based on Structural Similarity*

"Structural similarity" has served as a basis for selecting a lead compound.[206] The *Sanofi-Aventis* court further extends the "structural similarity" requirement to modification of a lead compound. For instance, in rejecting the defendant's arguments related to reducing Pgp-related drug resistance, the *Sanofi-Aventis* court criticized that Hait's article "studied phenothiazines, which are much smaller than taxanes and have a three-ring structure bearing no resemblance to taxanes."[207] Likewise, in reviewing the defendant's arguments about increasing lipophilicity, the *Sanofi-Aventis* court pointed to the fact that Lampidis' article "focused on positively-charged dyes and suggested that increasing lipophilicity of positively-charged molecules could be beneficial, but docetaxel is not positively charged."[208]

The *Sanofi-Aventis* court also highlighted the problems of those cited references. First, the *Sanofi-Aventis* court questioned that "despite the apparent interest in taxane analogs, not a single reference relied on by [the defendant] made simultaneous substitutions of any kind at C7 and C10."[209] Second, the *Sanofi-Aventis*

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[201] *Sanofi-Aventis U.S., LLC*, 933 F.3d at 1379-80.

[202] *Id*. at 1380.

[203] *Id*.

[204] *Id*.

[205] *Id*.

[206] *See* W. Nicholson Price II, *The Cost of Novelty*, 120 COLUM. L. REV. 769, 786-87 (2020) (discussing the Federal Circuit's lead compound analysis); *see also* Douglas L. Rogers, *Federal Circuit's Obviousness Test for New Pharmaceutical Compounds: Gobbledygook?*, 14 CHI.-KENT J. INTELL. PROP. 49, 83 (2014) (discussing the Federal Circuit's decision in *Otsuka Pharm. Co.*); *but see* Eli Lilly & Co. v. Zenith Goldline Pharm., Inc., 471 F.3d 1369, 1379 (Fed. Cir. 2006) ("And though olanzapine is also the adjacent homolog of Compound '222, patentability for a chemical compound does not depend only on structural similarity. . . . When claimed properties differ from the prior art, those differences, if unexpected and significant, may lead to nonobviousness.").

[207] Sanofi-Aventis U.S., LLC v. Dr. Reddy's Labs., Inc., 933 F.3d 1367, 1378 (Fed. Cir. 2019).

[208] *Id*.

[209] *Id*. at 1379.

court found nowhere in Ojima's article "investigated a methoxy-substituted taxane, at C10 or anywhere else."[210]

The *Sanofi-Aventis* approach is consistent with the Federal Circuit's precedent. In *Takeda Chemical Industries, Ltd.*, the patented compound was pioglitazone, an active ingredient of ACTOS® used for treating patients who suffer from Type 2 diabetes.[211] The asserted lead compound (compound b) had a pyridyl ring with a methyl (CH_3) group attached to the 6-position of the ring, while pioglitazone had a pyridyl ring with an ethyl (C_2H_5) group attached to the 5-position of the ring.[212] Although both compound b and pioglitazone belong to the same chemical class, thiazolidinediones, the Federal Circuit upheld the district court's nonobviousness conclusion.[213]

The question in *Takeda Chemical Industries, Ltd.* was whether there would have been a motivation to "both homologate the methyl group of compound b and move the resulting ethyl group to the 5-position on the pyridyl ring in order to obtain pioglitazone."[214] The first and second steps were referred to as "homologation" and "ring-walking," respectively.[215] The district court found no expectation that ring-walking would have improved efficacy and safety.[216]

Among other things, the district court considered the opinion of the defendant's expert expressing that the patentee "knew" the ring-walking idea.[217] However, the expert opinion was based on the efficacy data of phenyl compounds in one prior art reference (Sohda II paper).[218] The defendant also failed to show that "one skilled in the art would have understood that these results were transferable from a phenyl to a pyridyl compound[.]"[219] Thus, the district court discredited the expert opinion.[220]

On appeal, the *Takeda* court did not hold the district court's ring-walking findings clearly erroneous.[221] Therefore, the *Takeda* court implied that because of the structural difference between pyridyl and phenyl the obviousness analysis requires

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[210] *Id.*

[211] Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1352 (Fed. Cir. 2007).

[212] *Id* at 1354.

[213] *Id* at 1355.

[214] *Id* at 1360; *see also* Scott R. Conley, *Irrational Behavior, Hindsight, and Patentability: Balancing the "Obvious to Try" Test with Unexpected Results*, 51 IDEA 271, 290 (2011) ("To homologate" or "homologation" is defined as a reaction for converting a member of a chemical class by adding a carbon atom into the targeted functional group of a compound.). *See* M. Röper & H. Loevenich, *The Homologation of Methanol*, CATALYSIS IN C1 CHEMISTRY 105, 105 (W. Keim ed., D. Reidel Publishing Co. 1983).

[215] *Takeda Chem. Indus., Ltd.*, 492 F.3d at 1360.

[216] *Id.* at 1361; *see also* Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc., 417 F. Supp. 2d 341, 381 (S.D.N.Y. 2006) ("[the defendant] has not shown that one skilled in the art would have been motivated to move to pioglitazone by 'walking the ring.'").

[217] *Takeda Chem. Indus., Ltd.*, 492 F.3d at 1361.

[218] *See id.*; *see also* T. Sohda et al., *Studies on Antidiabetic Agents. II. Synthesis of 5–[4–(1–Methylcyclohexylmethoxy)–benzyl]thiazolidine–2,4–dione (ADD–3878) and its Derivatives*, 30 CHEM. PHARM. BULL. 3580 (1982). *See Takeda Chem. Indus., Ltd.*, 417 F. Supp. 2d at 350-51.

[219] *Takeda Chem. Indus., Ltd.*, 417 F. Supp. 2d at 382; *see also Takeda Chem. Indus., Ltd.*, 492 F.3d at 1361.

[220] *Takeda Chem. Indus., Ltd.*, 417 F. Supp. 2d at 382.

[221] *Takeda Chem. Indus., Ltd.*, 492 F.3d at 1362-63.

additional evidence to show what happened in a phenyl compound is expected to be repeated in a pyridyl compound.

E. *Implication II: Motivation Based on Test Data*

The *Sanofi-Aventis* court acknowledged that "taxane modifications were considered at C2, C4, C5, C7, C8, C9, C10, C11, C12, C13, C14, [C'2], and [C'3]" or that "taxane researchers investigated substitutions at many positions[.]"[222] However, the *Sanofi-Aventis* court found no clear error in the district court's conclusion that "it would not have been obvious to make simultaneous methoxy substitutions at C7 and C10 of docetaxel[.]" [223] Thus, the *Sanofi-Aventis* approach suggests that while chemical modifications at various positions of a lead compound may have been routine for an ordinary skilled organic chemist, proving obviousness requires more evidence to show that a specification modification would have been obvious.

Under the *Sanofi-Aventis* approach, a reason for simultaneously modifying specific positions to make a pharmaceutical compound depends on a scientific test for demonstrating that the anti-disease property may come from such modification. For instance, the *Sanofi-Aventis* court noted that "of the references that made individual methoxy substitutions at C7 or C10, none tested those taxane analogs against drug resistant cell lines or taught that the analogs would overcome drug resistance."[224]

The *Sanofi-Aventis* approach again followed the Federal Circuit's case law. In *Takeda Chemical Industries, Ltd.*, the Federal Circuit opined that the toxicity test data in Sohda II paper supported the district court's finding that "homologation had no tendency to decrease unwanted side effects"[225] and, therefore, that researchers would not have focused on the homologation of compound b.[226] A result of testing even forecloses a desire to modify a lead compound. For example, when analyzing the issue of homologation, the *Takeda* court emphasized that "several other compounds exhibited similar or better potency than compound b, and one compound in particular, compound 99, that had no identified problems differed significantly from compound b in structure."[227]

In *Bristol-Myers Squibb Co.*, the patent compound was entecavir (Figure 5(a)) used for treating hepatitis B under the trade name Baraclude®.[228] The alleged lead compound was 2'-CDG (Figure 5(b)), a potent antiviral carbocyclic nucleoside analog

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[222] Sanofi-Aventis U.S., LLC v. Dr. Reddy's Labs., Inc., 933 F.3d 1367, 1377-78 (Fed. Cir. 2019).

[223] *Id.*; *see also* Sanofi-Aventis U.S. LLC v. Fresenius Kabi USA, LLC, No. CV147869MASLHG, 2018 WL 9364037, at *11 (D.N.J. Apr. 25, 2018) ("Defendants, however, failed to demonstrate that a [person of ordinary skill in the art] would have been motivated to simultaneously modify docetaxel with a methyl ether at the C-7 and C-10 positions to arrive at cabazitaxel.").

[224] *Sanofi-Aventis U.S., LLC*, 933 F.3d at 1378.

[225] Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1360 (Fed. Cir. 2007) (quoting *Takeda Chem. Indus., Ltd., Inc.*, 417 F. Supp. 2d at 383).

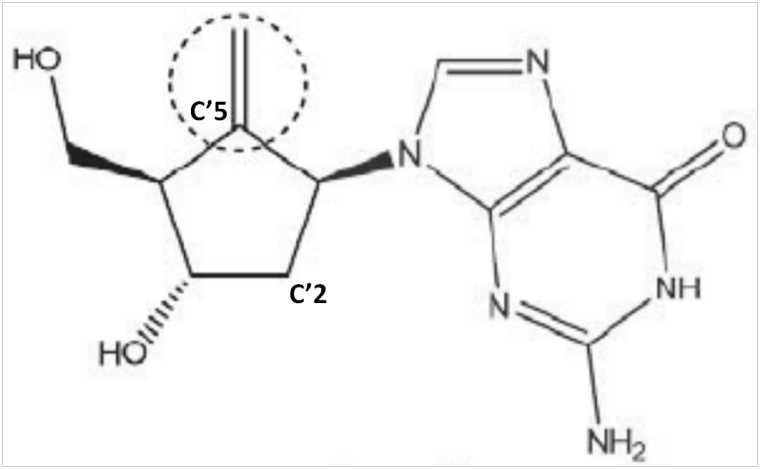
[226] *Takeda Chem. Indus., Ltd.*, 492 F.3d at 1360; *see also Takeda Chem. Indus., Ltd.*, Inc., 417 F. Supp. 2d at 383 ("One of ordinary skill in the art would therefore have been more likely to conclude from Sohda II that homologation had no tendency to decrease unwanted side effects and to focus research efforts elsewhere.").

[227] *Sanofi-Aventis U.S., LLC*, 933 F.3d at 1360-61.

[228] *See* Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc., 752 F.3d 967, 969 (Fed. Cir. 2014).

of deoxyguanosine.[229] 2'-CDG was structurally different from entecavir, because entecavir has a carbon-carbon double bond (exocyclic methylene group) at C'5 of the carbocyclic ring.[230]

The *Bristol-Myers* court agreed with the district court's opinion that in light of Madhavan 30 compound (Figure 5(c)), it would have been obvious to modify 2'-CDG to create entecavir.[231] Madhavan 30 compound came from a research effort focusing on nucleoside analogs composed of a carbocyclic ring and adenosine base.[232] Madhavan 30 compound was developed by substituting an exocyclic methylene group at C'5 position of the carbocyclic ring of aristeromycin.[233] Madhavan 30 compound showed improved antiviral activity over aristeromycin.[234] Thus, considering the fact that a chemist would have sought to make small, conservative changes to C'2 or C'5 of 2'-CDG's carbocyclic ring, the *Bristol-Myers* court concluded that an exocyclic methylene group would have been chosen to modify C'5 position.[235]



(a) Entecavir

[229] *Id.*

[230] *Id.* at 969-70.

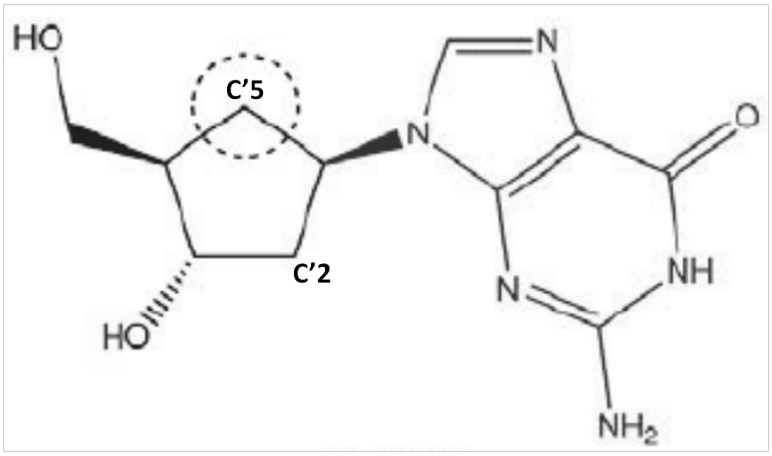
[231] *Id.* at 975-76.

[232] *Id.* at 971.

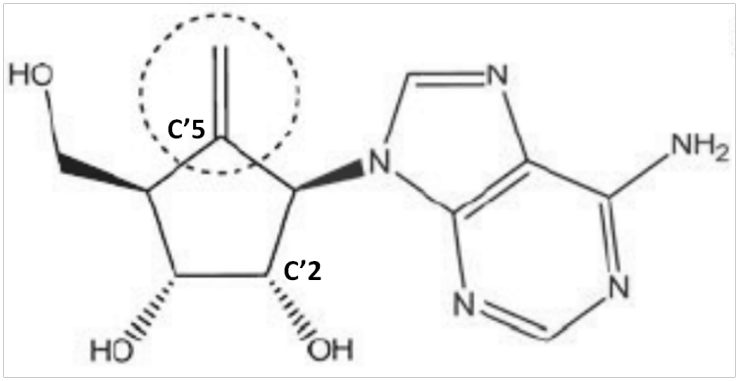
[233] Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc., 923 F. Supp. 2d 602, 628 (D. Del. 2013).

[234] Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc., 752 F.3d 967, 975 (Fed. Cir. 2014); *see also Bristol-Myers Squibb Co.*, 923 F. Supp. 2d at 628.

[235] *Bristol-Myers Squibb Co.*, 752 F.3d at 975-76; *see also Bristol-Myers Squibb Co.*, 923 F. Supp. 2d at 667-68 ("These selections equate to a small, finite number of changes to try to the lead compound, 2'-CDG. Specifically, it would leave six options to pursue: binding a fluorine atom up or down at the 2 prime or 5 prime position and binding a double-bonded carbon atom30 at the 2 prime or 5 prime position (although, as previously noted, Glaxo researchers had already made a compound with a fluorine atom pointing up at the 2 prime position of 2'-CDG).").



(b) 2'-CDG



(c) Madhavan 30 Compound

Figure 5

V. LEAD COMPOUND ANALYSIS FOR ONGOING DRUG DEVELOPMENT

As explained in Part IV, the *Sanofi-Aventis* approach requires an obvious path from the lead compound (paclitaxel or docetaxel) to the patented compound (cabazitaxel) be based on a scientific expectation. The scientific expectation comes from both the structural similarity of tested prior art compounds and the test results of these compounds.[236] Part V further demonstrates that the *Sanofi-Aventis* approach follows the *KSR* Court's principles and is beneficial to ongoing drug development.

[236] *See supra* Part IV.D & E.

A. *Pro-Drug Discovery Approach*

Paclitaxel and docetaxel are two cancer drugs developed by two different research groups in United States and France, respectively.[237] Both drugs are based on the same precursor 10-DAB.[238] While paclitaxel was developed by BMS, docetaxel was developed by PRP that later became Sanofi-Aventis.[239] Sanofi-Aventis eventually created cabazitaxel.[240]

The development history of paclitaxel, docetaxel and cabazitaxel stands for a case of the competition of drug discovery between two pharmaceutical companies.[241] These drugs belong to the same class of taxanes.[242] Researchers from two companies have published academic articles or filed patent applications for taxane compounds.[243] So, the information given in those public documents may provide a "good reason to pursue the known options [of functional group modification,]"[244] especially when the research group of cabazitaxel utilized paclitaxel or docetaxel as a starting point.[245] But, the question is what the motivation or reason behind such a pursuit is.

A pharmaceutical compound is created only to treat a disease or condition, but "design incentives" may come not only from acquiring therapeutically-related properties but also from, nowadays, improving physiochemical properties. [246] Particularly, cabazitaxel came from a research intended to treat drug-resistant tumors.[247] The research ended up with simultaneous methoxy substitutions at C7 and C10 positions of docetaxel.[248]

If the idea of simultaneous methoxy substitutions at C7 and C10 positions was an improvement, then the question is whether simultaneous methoxy substitutions at C7 and C10 positions would have been considered as "the predictable use of prior

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[237] Vivien Walsh & Muriel Le Roux, *Contingency in Innovation and the Role of National Systems: Taxol and Taxotère in the USA and France*, 33 RESEARCH POLICY 1307, 1307-08 (2004).

[238] *See supra* Part I.

[239] *See* Yeda Research and Dev. Co. v. Imclone Sys. Inc., 443 F. Supp. 2d 570, 578 (S.D.N.Y. 2006) ("In 1990, the Rorer Group merged with the health care arm of Rhone-Poulenc, forming Rhone-Poulenc Rorer, Inc. ('RPR'). Nine years later, RPR merged with Hoechst-Marion-Roussel to form Aventis. In 2004, Aventis was acquired by Sanofi-Synthelabo, forming the sanofi-aventis Group. Defendant Aventis Pharmaceuticals is a wholly-owned subsidiary of the sanofi-aventis Group.").

[240] *See supra* Part IV.A.

[241] *See supra* Part I.

[242] *See supra* Part I.

[243] *See supra* Part IV.B.

[244] KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007).

[245] *See* Sanofi-Aventis U.S. LLC v. Fresenius Kabi USA, LLC, No. CV147869MASLHG, 2018 WL 9364037, at *4 (D.N.J. Apr. 25, 2018) ("Around 1989, Sanofi launched a medicinal chemistry program to search for taxane analogs to treat cancers. The program used existing taxanes, docetaxel, which was then under development by Sanofi, and paclitaxel, as reference compounds." (internal citations omitted)).

[246] Margaret S. Landis et al., *Commentary: Why Pharmaceutical Scientists in Early Drug Discovery Are Critical for Influencing the Design and Selection of Optimal Drug Candidates*, 19(1) AAPS PHARMSCITECH 1, 1-3 (2018).

[247] *See supra* Part I.

[248] *See supra* Part IV.A.

art elements according to their established functions."[249] As the *KSR* Court has required, three factors must be evaluated together: (1) "interrelated teachings of multiple patents"; (2) "the effects of demands known to the design community or present in the marketplace"; and (3) "the background knowledge possessed by a person having ordinary skill in the art."[250] Unfortunately, the defendant in *Sanofi-Aventis U.S., LLC* failed to present any scientific evidence, such as test data in those prior art references or non-conclusory, specified expert testimony, to show the teaching or knowledge of the effect of simultaneous C7 and C10 methoxy substitutions on drug-resistant tumor cells.[251]

The *KSR* Court also required that the obviousness analysis "should be made explicit."[252] However, the explicit analysis can rely on "the inferences and creative steps that a person of ordinary skill in the art would employ."[253] Unfortunately, in *Sanofi-Aventis U.S., LLC*, the prior art references disclosing taxane analogs with an individual methoxy substitution at C7 or C10 position did not provide any test data on drug-resistant cell lines or teach that those taxane analogs would overcome drug resistance.[254] Therefore, no inference or creative step could be drawn from these references.

In conclusion, the *Sanofi-Aventis* approach follows the *KSR* Court's principles and establishes an evidentiary standard for determining the nonobviousness requirement of pharmaceutical compound patents. With that, a pharmaceutical compound evolving from its ancestor compounds can be patentable under 35 U.S.C. § 103, if the effect of an alleged modification was unknown back then.

B. *Hindsight-Free Approach*

As Taryn Elliott contended, "[p]ost-*KSR* courts maintain that the Non-Rigid TSM rationale remains the primary guarantor against a nonstatutory hindsight bias because the Non-Rigid TSM rationale ensures that the obviousness determination is based on evidence."[255] Focusing on the test result of a prior art compound has guided the determination of whether an alleged modification would have been obvious.[256] The *Sanofi-Aventis* approach can further avoid a hindsight-based analysis of obviousness.

While recognizing that Golik's patent disclosed "a taxane analog with a methylthiomethoxy [(H_3C-S-H_2CO-)] substitution at C7, which had promising qualities against drug-resistant cell lines[,]" the *Sanofi-Aventis* court rejected the defendant's attempt to extend the disclosure to the teaching of making a methoxy

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[249] *KSR Int'l Co.*, 550 U.S. at 417.

[250] *Id.* at 418.

[251] Sanofi-Aventis U.S., LLC v. Dr. Reddy's Labs., Inc., 933 F.3d 1367, 1378-80 (Fed. Cir. 2019).

[252] *KSR Int'l Co.*, 550 U.S. at 418.

[253] *Id.*

[254] *Sanofi-Aventis U.S., LLC*, 933 F.3d at 1378.

[255] Taryn Elliott, *Post-KSR Obviousness: The Effects of the Patent and Trademark Office's Exemplary Rationales on Patent Litigation*, 16 GEO. MASON L. REV. 1011, 1088-89 (2009).

[256] *See supra* Part IV.E.

(H_3CO-) substation at C7.[257] The defendant's argument seemed to rely on structural similarity between methylthiomethoxy and methoxy, but the *Sanofi-Aventis* court criticized the argument as "little more than hindsight."[258] As a result, the *Sanofi-Aventis* court not only affirmed the district court's finding "no evidence that the methoxy group would provide a similar benefit as the sulfur-containing methylthiomethoxy group[,]" but also pointed out "the absence of any evidence showing equivalent properties of a methoxy substitution[.]"[259]

The *Sanofi-Aventis* court also denied the defendant's another attempt to rely on Ojima's article allegedly teaching the benefits of an acetoxy group at C10 against drug-resistant cells.[260] The defendant argued that Ojima's article would have motivated a methoxy substitution at C10.[261] But, the *Sanofi-Aventis* court again found "no non-conclusory evidence that the methoxy group would have the same purported benefits as the acetoxy group[.]"[262]

However, the *Sanofi-Aventis* approach is not a rigid test, because the *Sanofi-Aventis* court only required, for example, "persuasive explanation of how the methoxy group, which was not tested in [Ojima's article], would be a more conservative choice than the C10 acetoxy already present in the FDA-approved drug paclitaxel."[263] That is, the *Sanofi-Aventis* approach accepts the source of motivation from something other than Ojima's article. In fact, the *Sanofi-Aventis* approach complies with the *KSR* Court's opinion that "[a] factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning."[264]

C. *Flexible TSM Test*

The *KSR* Court rejected the Federal Circuit's rigid approach to the TSM test and reasoned that "[its] cases have set forth an expansive and flexible approach[.]"[265] However, the Supreme Court did not fully abrogate the TSM test.[266] Some commentators have noted that the Federal Circuit in the post-*KSR* era has adopted a modified TSM test.[267] For instance, Emer Simic stated that the Federal Circuit still

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[257] *Sanofi-Aventis U.S., LLC*, 933 F.3d at 1379.

[258] *Id.*

[259] *Id.*

[260] *See id.*

[261] *See id.*

[262] *Sanofi-Aventis U.S., LLC*, 933 F.3d at 1379.

[263] *Id.* at 1379-80.

[264] KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007).

[265] *Id.* at 415.

[266] Thomas G. Hungar & Rajiv Mohan, *A Case Study Regarding the Ongoing Dialogue Between the Federal Circuit and the Supreme Court: The Federal Circuit's Implementation of KSR v. Teleflex*, 66 SMU L. REV. 559, 562 (2013).

[267] *See* Emer Simic, *The TSM Test Is Dead! Long Live the TSM Test! The Aftermath of KSR, What Was All the Fuss About?*, 37 AIPLA Q.J. 227, 249 (2009) (discussing Takeda Chemical Industries, Ltd.); *see also* Elliott, *supra* note 255, at 1087-89 (addressing how the Federal Circuit adopts a Non-Rigid TSM rationale); *see also* Hungar & Mohan, *supra* note 266, at 562-64 (discussing how the Federal Circuit improved the flexibility of the TSM test); *see also* Mark D. Janis, *Tuning the*

requires "an explicit reason for why a certain option was 'obvious to try' before the court will determine an invention to be obvious."[268]

In fact, the *KSR* Court allowed the Federal Circuit to develop a flexible version of the TSM test.[269] But, for pharmaceutical compound patents, Prof. Douglas L. Rogers concluded that "[a]lthough some of these cases refer to applying the test 'flexibly,' they are really referring to applying the TSM test flexibly to determine if prior art showed the lead compound and each subsequent step up to the final compound[.]"[270] The *Sanofi-Aventis* approach may reinstate Prof. Rogers' conclusion.

The *Sanofi-Aventis* court defined what a flexible standard means by distinguishing itself from the *Bristol-Myers* decision.[271] First, the *Sanofi-Aventis* court considered the *Bristol-Myers* decision as affirming "a district court's conclusion that it would have been obvious to make a single chemical change to a lead compound where there were a 'small, finite number of changes to try,' and the particular claimed change had already been shown to have desirable properties in a similar context."[272] Second, the *Sanofi-Aventis* court emphasized that "the district court's findings in this case are quite different" from *Bristol-Myers Squibb Co.*[273] The *Sanofi-Aventis* court noted that "numerous docetaxel modifications were under investigation, and there was no showing that making individual or simultaneous methoxy substitutions at C7 and C10 improved activity against drug-resistant cells, the sole motivation relied on by [the defendant]."[274] Therefore, the *Sanofi-Aventis* court opined that the present case "demand[s] a different outcome."[275]

The *Bristol-Myers* decision actually follows the *KSR* Court's notion that "[w]hen there is a design need or market pressure to solve a problem and there are *a finite number of identified, predictable solutions*, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp."[276] However, the *Sanofi-Aventis* court characterized *Bristol-Myers Squibb Co.* as providing "a bright-line legal rule [which] would be *inconsistent* with the flexible analysis inherent to the highly contextual obviousness inquiry."[277] Consequently, the *Sanofi-Aventis* court rejected a view that "small changes to a compound are necessarily *prima facie* obvious."[278]

Obviousness Inquiry After KSR, 7 WASH. J.L. TECH. & ARTS 335, 342-45 (2012) (describing the Federal Circuit's flexible TSM test after KSR); *see also* Jason Rantanen, *The Federal Circuit's New Obviousness Jurisprudence: An Empirical Study*, 16 STAN. TECH. L. REV. 709, 752-57 (2013) (illustrating a trend of the Federal Circuit's new TSM test); *see also* Rogers, *supra* note 206, at 81-90 (showing the Federal Circuit's attempts to distinguish KSR).

[268] Simic, *supra* note 267, at 249.

[269] Hungar & Mohan, *supra* note 266, at 562-63.

[270] Rogers, *supra* note 206, at 89.

[271] Sanofi-Aventis U.S., LLC v. Dr. Reddy's Labs., Inc., 933 F.3d 1367, 1380 (Fed. Cir. 2019).

[272] *Id.* (citing *Bristol-Myers Squibb Co.*, 752 F.3d at 975-76).

[273] *See id.*

[274] *Id.*

[275] *Id.*

[276] KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 421 (2007) (emphasis added).

[277] *Sanofi-Aventis U.S., LLC*, 933 F.3d at 1380 (citing *KSR Int'l Co.*, 550 U.S. at 415) (emphasis added).

[278] *Id.*

Nonetheless, the *Sanofi-Aventis* approach does not contrast with the *KSR* Court's notion, because the situation of numerous modification options (e.g., C2, C4, C5, C7, C8, C9, C10, C11, C12, C13, C14, C'2, and C'3),[279] rather than "a finite number of identified, predictable solutions," in the present case would not have led a person of ordinary skill to reasonably pursue individual or simultaneous methoxy substitutions at C7 and C10. Therefore, it is fair to say that the *Sanofi-Aventis* approach is a flexible TSM test.

VI. CONCLUSION

Whether a pharmaceutical compound acquires patentability under 35 U.S.C. § 103 depends on whether one of ordinary skill in the art would have "a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success."[280] Courts may also adjudicate whether one of ordinary skill in the art would have selected the alleged compound as a lead compound.[281] Alternatively, courts may ask only whether one of ordinary skill in the art would have modified "a known compound in a particular manner to establish prima facie obviousness of a new claimed compound."[282]

The *Sanofi-Aventis* decision advances the nonobviousness standard for pharmaceutical compound patents by requiring showing a scientific expectation. That is, a defendant must base its obviousness reasoning on both the structural similarity of prior art compounds tested and the test results of these compounds.

Under the *Sanofi-Aventis* approach, a pharmaceutical compound is more likely patentable under 35 U.S.C. § 103, even though it is derived from its ancestor compounds. These ancestor compounds may have been published or patented, so that various functional groups on them become prior art structures. However, as long as these functional groups are not shown by test data to connect to any improved property of the claimed compound, obviousness cannot be sustained.

Lastly, although the *Sanofi-Aventis* approach requires an evidence-based obviousness analysis, it is not a rigid test opposed by the *KSR* Court. The *Sanofi-Aventis* approach still accepts non-conclusory expert opinions. On the other hand, a hindsight-based obviousness analysis can be avoided when modification options based on structural similarity are lack of a sound explanation.

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[279] *See id.* at 1377.

[280] Otsuka Pharm. Co. v. Sandoz, Inc., 678 F.3d 1280, 1292 (Fed. Cir. 2012).

[281] *Id.* at 1291.

[282] Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd., 492 F.3d 1350, 1356-57 (Fed. Cir. 2007).