המפגש המקצועי של קהילת עורכי הפטנטים בישראל

רפואה מותאמת אישית:
התפתחויות בארה"ב בעקבות
Vanda v. West-Ward

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קבוצת ריינהולד כהן

In recent years there has been a dramatic rise in the number of drugs approved by health authorities that have a personalized healthcare approach.

The aim is to target the right treatment to the right patient, typically by using a diagnostic test (companion diagnostic test) for one or more biomarkers indicative of drug response

What is personalized medicine?

- The ultimate goal of personalized medicine is to provide a patient with the ideal treatment, optimized to the patient's *individual* genome, to promote effective, efficient, and tailored care.
- To know which drugs will be helpful in treatment and how to mitigate potentially serious side effects of chosen drugs
- To determine a dosing regimen which is tailored to the patient's particular needs

Targeted medicine in contrast to the hit and miss approach

- *Herceptin*, given specifically to patients with *HER2-positive* breast cancer in combination with chemotherapy. This personalized treatment regimen nearly doubled the time before relapse.
- *Gleevec* is used to treat chronic myeloid leukemia in patients which are positive for the marker BCR-ABL, which has increased life expectancy from 5% to 95% at 5 years.
- Prediction of correct dosing. The CYP 450 enzyme and its application to *Coumadin/warfarin* therapy. Hospitalizations due to stroke were reduced by 30%.

The “Law of Nature” challenge

- Personalized medicine patents typically include measuring something naturally present in the body.
- In *Mayo v. Prometheus*, decided in 2011, the US Supreme Court declared patent ineligible claims directed towards diagnostic methods useful in the optimization of drug dosage for an individual patient, based on the Court’s determination that the claims were directed to a law of nature.
- The US Supreme Court’s opinion in *Mayo v. Prometheus*, and the USPTO guidance which followed, interpreted ***101*** broadly, extending significantly the definitions of natural phenomena and laws of nature and thereby created a serious threat to biotech patents, especially in this field.

לשכת עורכי הפטנטים בישראל

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Winds of change

The Vanda Patent

US 8,586,610 issued November 13, 2013

An example of a personalized medicine claim

Iloperidone - background

- Iloperidone is an antipsychotic drug approved by the FDA in 2009 for the treatment of schizophrenia and marketed by Vanda under the tradename Fanapt.
- CYP2D6 is the cytochrome P450 2D6 gene, which encodes an enzyme known to metabolize iloperidone
- A subject that has lower than normal CYP2D6 enzyme activity, which means that iloperidone is inefficiently metabolized and persists longer in the body, is defined as a “poor metabolizer”.
- The resulting increased drug exposure can lead to physiological complications such as prolongation of the time interval between the Q and T waves of the heart rhythm, which may lead to serious cardiac problems.

Claim 1

A method for treating a patient with iloperidone, wherein the patient is suffering from schizophrenia, the method comprising the steps of:
determining whether the patient is a CYP2D6 poor metabolizer by:
obtaining or having obtained a biological sample from the patient; and
performing or having performed a genotyping assay on the biological sample to determine if the patient has a CYP2D6 poor metabolizer genotype; and
if the patient has a CYP2D6 poor metabolizer genotype, then internally administering iloperidone to the patient in an amount of 12 mg/day or less, and
if the patient does not have a CYP2D6 poor metabolizer genotype, then internally administering iloperidone to the patient in an amount that is greater than 12 mg/day, up to 24 mg/day, wherein a risk of QTc prolongation for a patient having a CYP2D6 poor metabolizer genotype is lower following the internal administration of 12 mg/day or less than it would be if the iloperidone were administered in an amount of greater than 12 mg/day, up to 24 mg/day.

Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.

- Upon filing the New Drug Application (NDA) for Iloperodine Vanda listed its composition of matter patent (Reissue 39,198) in the Orange Book. [This patent expired November 15, 2016].
- In 2013, the generic drug company West-Ward filed an Abbreviated new Drug Application (ANDA) seeking approval to manufacture and sell a generic version of Iloperidone.
- While the ANDA was pending, the USPTO issued Vanda's US 8,586,610 patent (November 2013)
- Shortly afterwards Vanda listed the '610 patent in the Orange Book
- West-Ward amended the ANDA to include a certification that the '610 patent was invalid or not infringed by the generic drug

Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.

- Vanda sued West-Ward for infringement of the '610 patent in the district court under the Hatch-Waxman Act.
- West-Ward's defense focused on two issues (1) amending the ANDA is not an infringement since the '610 patent issued after the original ANDA filing and (2) the '610 patent is invalid under 101.
- The district court concluded that (1) an amended Paragraph IV certification addressing a subsequent patent could be an infringing act and (2) the '610 claims are valid.
- As a result, the district court found that the proposed marketing of the generic iloperidone would infringe the '610 patent and enjoined West-Ward from any manufacture, use.. of iloperidone prior to the expiration of the '610 patent (2027).
- West-Ward filed an Appeal.

Vanda Pharms. Inc. v. West-Ward Pharms. Int'l Ltd.

- On April 13, 2018, the Court of Appeal of the Federal Circuit **affirmed the validity of US 8,586,610**.
- The Court found that the claims are not drawn to a law of nature under 101.

This is the first time that the Federal Circuit addresses this question heads-on and answers it in the affirmative.

The Federal Circuit's Analysis of the Patent Eligibility Issue

- The Federal Circuit applied the Mayo/Alice two-step framework to determine patent eligibility under 101:
  - Is the claim at issue directed to a patent ineligible concept, i.e. a law of nature, natural phenomenon or abstract idea; and, if this is the case,
  - Does the claim incorporate additional elements that transform the claim into a patent eligible application of that concept. Establishing an inventive concept, "significantly more".

Vanda v. West-Ward:
Dosage Adjustment Claims are Patent Eligible

- In a split decision, a two-judge majority held that under step 1 of the framework, Vanda's claim is not directed to a patent ineligible concept.
- The real challenge for the majority was to distinguish Vanda's claim from claims ruled patent ineligible by the Supreme court in *Mayo*.

Representative claims

Vanda	*Mayo*
A method for treating a patient with iloperidone, wherein the patient is suffering from schizophrenia, the method comprising the steps of: determining whether the patient is a CYP2D6 poor metabolizer by: obtaining or having obtained a biological sample from the patient; and performing or having performed a genotyping assay on the biological sample to determine if the patient has a CYP2D6 poor metabolizer genotype; and if the patient has a CYP2D6 poor metabolizer genotype, then internally administering iloperidone to the patient in an amount of 12 mg/day or less, and if the patient does not have a CYP2D6 poor metabolizer genotype, then internally administering iloperidone to the patient in an amount that is greater than 12 mg/day, up to 24 mg/day, wherein a risk of QTc prolongation for a patient having a CYP2D6 poor metabolizer genotype is lower following the internal administration of 12 mg/day or less than it would be if the iloperidone were administered in an amount of greater than 12 mg/day, up to 24 mg/day.	A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising: (a) administering a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and (b) determining the level of 6-thioguanine or 6-methyl mercaptopurine in said subject having said immune-mediated gastrointestinal disorder, wherein the level of 6-thioguanine less than about 230 pmol per 8×108 red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and wherein the level of 6-thioguanine greater than about 400 pmol per 8×10^8 red blood cells or a level of 6-methyl mercaptopurine greater than about 7000 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

Points of difference between Vanda and Mayo

- In Vanda “A method of treating” v in Mayo “A method of optimizing therapeutic efficacy”
- In Vanda, first determining whether the patient is a poor metabolizer by performing a genotyping assay and next administering the appropriate dosage of the drug (treating) v in Mayo, first administering a drug, monitoring its level and next determining whether the treatment should be adjusted “wherein the level.. is greater.. indicates a need to decrease”

The decision

- The majority decision was written by Judge Lourie, a former patent attorney at a pharmaceutical company, which is knowledgeable and attuned to the needs of the biopharma industry.
- The Federal Circuit explained, that unlike *Mayo*, the patent claims here recite the steps of carrying out a **dosage regimen** based on the results of the genetic test.
- "At bottom, the claims here are directed to a specific method of treatment for specific patients using a specific compound at specific doses to achieve a specific outcome."
- Myriad irrelevant - The Court explained that the case of *Myriad* noted that "method claims" and "patents on new applications of knowledge about [particular] genes" were "not implicated by [its] decision" [quoting from the *Myriad* decision]
- The decision reflects the wish to support patenting to overturn the effects of the decision in Mayo
- One dissent (out of three) by Chief Judge Proust, who asserted that the additional "action step" should have been found insufficient to render the claim patent eligible, given the striking similarity to *Mayo*.

Interim remarks

- Vanda is Good News for molecular diagnostics/ personalized medicine/ patients
- The language of the decision is general and thus may be applicable to many other cases. Importantly the decision refers to step 1 of the framework of analysis.
- However, it may not be the last word. There was a dissent supported by well-reasoned arguments.
- The decision may be reversed upon reconsideration by the *en banc* court, by a decision in another case, or by the Supreme Court which may choose to get involved and overturn the decision

Effect of Vanda on subsequent decisions – the Endo case

- **Endo** owns a patent that covers a method of using oxymorphone to treat pain in patients with impaired kidney function.
- The method includes a step of measuring the patient's kidney function and orally administering, depending on the patient's creatinine clearance rate, a lower dosage of the drug based upon the concentration of the drug within the patient's blood stream
- Endo (and Mallinckrodt) sued Actavis for infringement . Actavis in return moved to dismiss Endo's claims as ineligible under 101.
- The magistrate judge recommended granting Actavis' motion.
- The district Court agreed with the Magistrate Judge.
- In a decision given March 28, 2019, the **Federal Circuit** reversed the District Court's decision, and concluded that the claims were directed to a patent-eligible method of using oxymorphone to treat pain in a renal impaired patient, based among others on the decision in Vanda.

Effect of Vanda on MPEP
USPTO - October 2019 Patent Eligibility Guidance Update

- Subject matter eligibility guidance explains how US Office personnel including patent examiners should evaluate claims for patent subject matter eligibility under 35 U.S.C. 101.
- Example 43: Treating kidney disease
- **Relevant case law**: • Mayo v. Prometheus Laboratories, Inc. (2012) • Endo Pharmaceuticals Inc. v. Teva Pharmaceuticals USA Inc., (Fed. Cir. 2019) • Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals International Ltd. (Fed. Cir. 2018) • Rapid Litigation Management Ltd. v. CellzDirect, Inc. (Fed. Cir. 2016)

Clear guidelines for patent eligible personalized medicine claims

Example 43 - Claims

1. A **treatment method** comprising:

(a) calculating a ratio of C11 to C13 levels measured in a blood sample from a patient diagnosed with Nephritic Autoimmune Syndrome Type 3 (NAS-3) to identify the patient as having a nonresponder phenotype;

(b)administering a treatment to the patient having a non-responder phenotype. ***NO [Judicial exception + the practical application is vague]***

2. The method of claim 1, wherein the treatment is a non-steroidal agent capable of treating NAS-3. ***YES***

3. The method of claim 1, wherein the treatment is rapamycin. ***YES***

4. The method of claim 1, wherein the treatment is a course of plasmapheresis. ***YES***

5. A treatment method comprising administering rapamycin to a patient identified as having Nephritic Autoimmune Syndrome Type 3 (NAS-3). ***YES***

The challenge – who *infringes?*

- In the screen + treat cases (involving a diagnostic company and a drug producing company), multiple people/entities perform the steps included in the claim, e.g.:
  - A diagnostic company sells the diagnostic kit;
  - A technician runs the test;
  - A drug company sells the drug;
  - A physician prescribes and/or administers the treatment;

  Diagnostic kits and drugs are usually produced and sold by different companies. Infringement is therefore divided among multiple actors.

The addition of a treatment step to a diagnostic method claim creates substantial enforcement issues

Divided infringement cases

- In the past, a patent directed to multiple actors could only be infringed if a single party was shown to exercise control over every step of the claimed method.
- Under this standard it would be practically impossible to establish **direct infringement** by a diagnostic company of a claim reciting a treatment step.
- This changed following a Federal Circuit decision in Akamai v. Limelight (2015) which clarified the requirements to bring an infringement claim in divided infringement cases.
- Under Akamai an agency relationship is not necessarily required, e.g. an entity can be held "responsible for other's performance of method steps… where the actors form a **joint enterprise**.
- However, proving the existence of a joint enterprise is not trivial.

And what about Indirect Infringement?

- In order for the patent owner to establish indirect infringement under a theory of inducement (induced infringement), he must first establish direct infringement by someone, e.g. a doctor, and show evidence of a specific intent on the part of the accused diagnostic or drug company to induce infringement by that doctor.
- Easier to prove in the case of a generic drug company that may be obliged to indicate on the drug's label that the drug should be used only following the performance of a diagnostic assay. Such recommendation can be regarded as an inducement of the doctor to perform an infringing act.
- More complicated is the reverse case when the accused is the diagnostic company, in which case it would be more difficult to prove inducement of the doctor to perform a treatment step.

A word about the EPO

- In May 2019 The technical board of appeal has issued a decision in T0694/16 relating to personalized medicine.
- The issue at stake was **novelty**. Namely, to determine whether patients displaying the markers were present among a population of previously treated patients and were already "inevitably" or "inherently" treated.
- **The Headword of Decision T 694/16 states:**

If a claim is directed to a known compound or composition for use in a therapeutic method of treatment or prevention of a disease, and the claim specifies that the subject to be treated displays a **clearly** defined and **detectable** marker, which is not displayed by all subjects affected by or likely to develop that disease, then the **purposive** selection of the patients displaying the marker for the specified treatment is a functional feature characterizing the claim. (**emphasis** added).

An Example of a personalized medicine claim

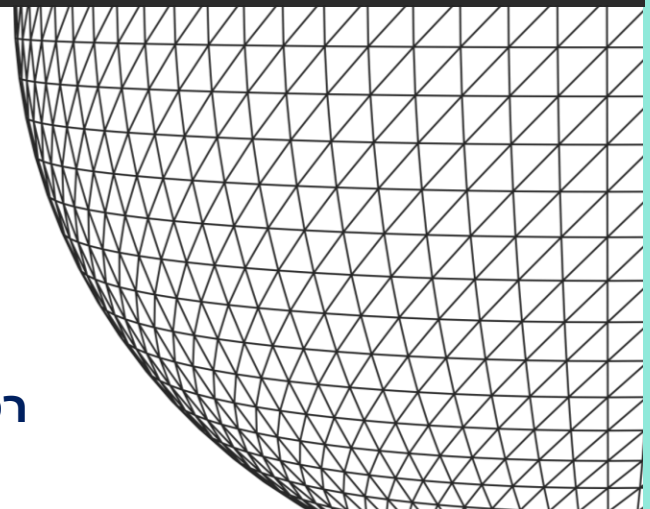
1. Composition comprising (a) one or more omega-3 fatty acids selected from DHA, DPA and EPA, (b) uridine selected from the group of uridine, deoxyuridine, uridine phosphates, uracil and acylated uridine derivatives, and (c) choline and/or phosphatidylcholine, wherein the composition further includes vitamin B12 and folate, for use in the prevention or delay of the onset of dementia in a person having characteristics of a prodromal dementia patient, wherein said characteristics comprise at least:
- a level of more than 350 ng Total-tau per litre cerebrospinal fluid (CSF); and
- a weight ratio of abeta-42/Phospho-tau-181 of less than 6.5 in CSF."

Concluding remarks

- Vanda, Endo, and the amended MPEP signal a change in attitude in the US towards personalized medicine claims
- Permissive language is clearer in both US and Europe
- Challenges:
  - The patenting of diagnostic claims per se (or how do we overcome the 101 obstacle when no treatment step can be added) Voices are heard that a legislative change must take place.
  - Infringement

Reinhold Cohn

Thank you!



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