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Patentability of inventions relating to methods of treatment - the way of protecting a medical use in the context of different patent systems

Patentability issues in the fields of pharmacy and biotechnology
9 May 2018, Warsaw, Poland

Topics:

- **Drug development and the ways of providing exclusivity**
- **Why we need second medical use claims — drug repurposing and personalized medicine**
- **Different ways of protecting a medical use**
- **Practice in selected jurisdictions**
- **Cases from our practice and tips for Polish applicants**

Drug development and the ways of providing exclusivity

Typical stages of drug development :

1) **pre-discovery stage** - researchers work on understanding a particular disease;

2) drug discovery - in which scientists identify a target or a way to combat the disease e.g. one compound from thousands that can be effective for treatment of a particular disease;

3) pre-clinical testing – mandatory studies in animals to determine the **toxicity** of the drug;

4) phase one clinical trials - with healthy human volunteers - to see if the drug is safe;

5) phase two clinical trials - tested on small numbers of patients to see if it's effective;

6) phase three clinical trials - provide evidence of effectiveness min. 1000 patients;

7) final (phase fourth) clinical trials - numbers involved, need to produce high quality pure material in large quantities;

8) regulatory authorities for **marketing authorization approval**,

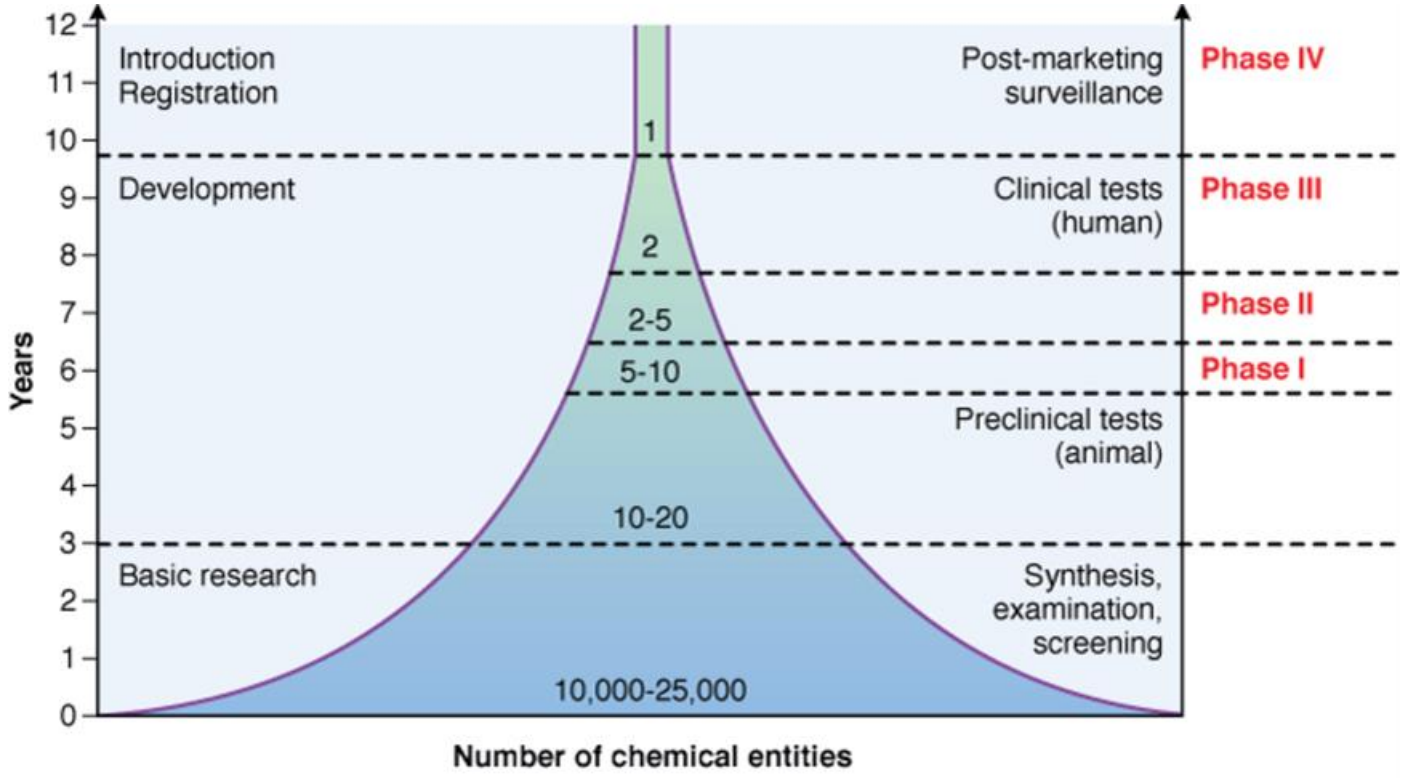
9) medicine is made **available** on market to **patients**.

10) Post approval development - studies to test new indications, formulations, and dosage etc.

(based on Kim Thomas, March 2016, Healthcare Network, Medicines and treatments, „ The price of health: the cost of developing new medicines")

Drug development and the ways of providing exclusivity

Just **ONE** in **10000** drug candidates makes it all the way from the drug discovery phase to licensing approval



Source: Brunton LL, Chabner BA, Knollmann BC: *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition:* www.accessmedicine.com

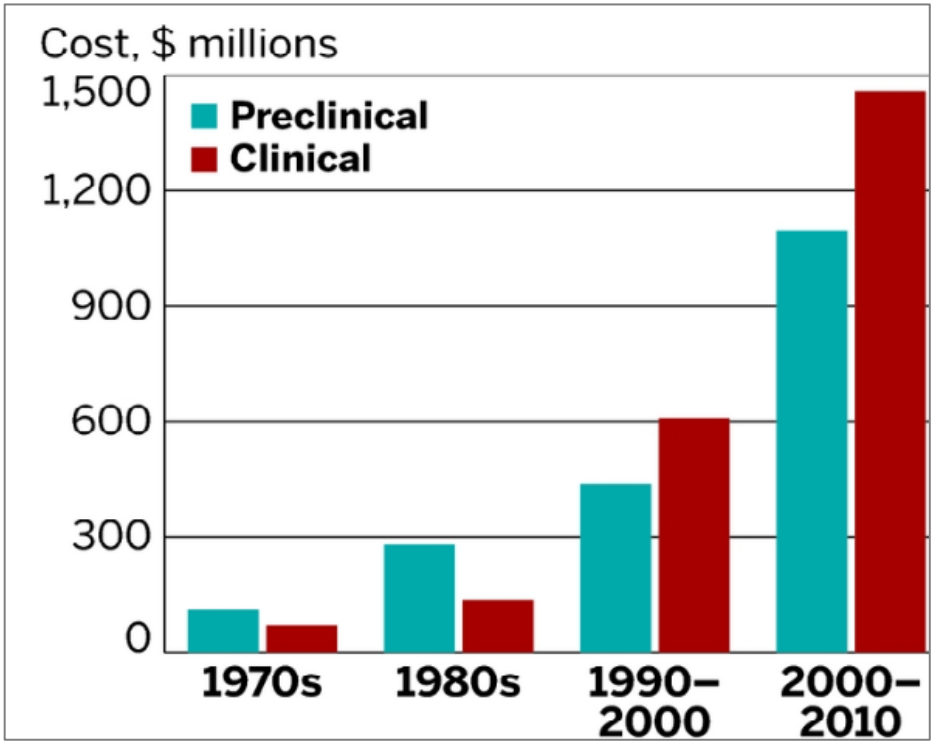
Pharmaceutical companies complain that drug development :

- **can take 12 or more years** from the initial discovery stage to licensing approval, with very high costs involved

Drug development and the ways of providing exclusivity

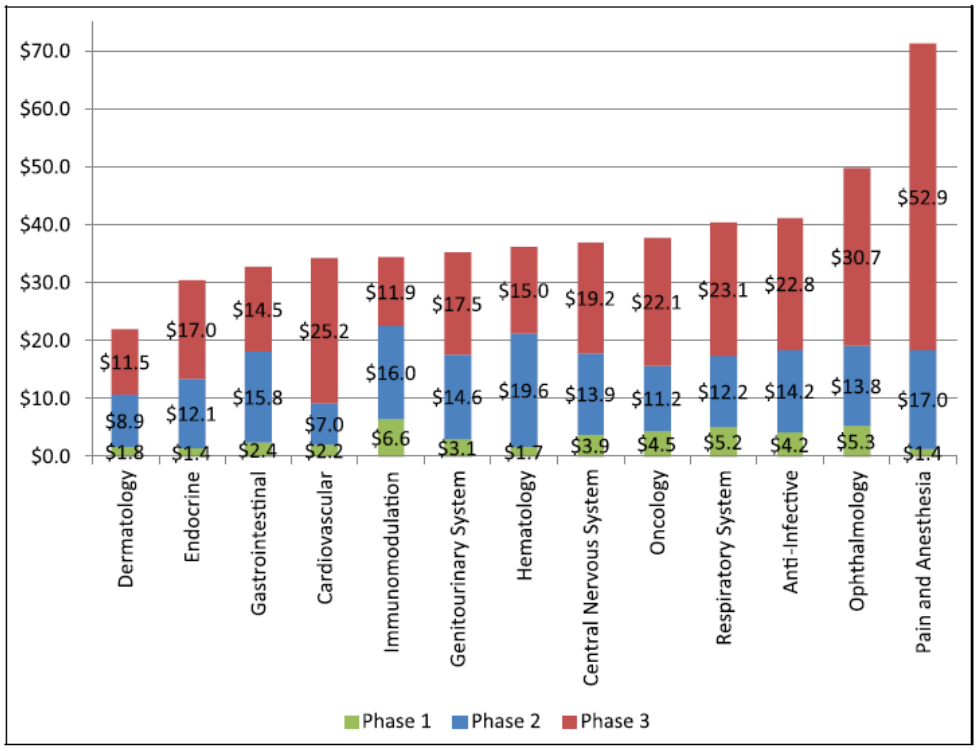
Drug development :

- **costs estimated at £1.15 bilion per drug** *(according to The Association of the British Pharmacuetical Industry);*
- With postapproval development a life-cycle cost of **$ 2.9 bilion**;
- Cost of developing a prescription drug that gains market approval has a 145% increase, correcting for inflation (*according to* CSDD, within 10 years).



The cost of developing a new drug has skyrocketed since the 1970s.

Source: Tufts Center for the Study of Drug Development (CSDD) , Rick Mullin, Chemical & Engineering News, November 24, 2014



Costs by therapeutic area and phase (in US$ million).

Source: „Key cost drivers of pharmaceutical clinical trials in the United States". Aylin S, et al., Clinical Trials 2016, Vol. 13(2) 117–126

Drug development and the ways of providing exclusivity

Pharmaceutical companies focus research on diseases they can profit from:

like chronic diseases (a drug taken for a long time e.g. diabetes for the rest of a patient's life) or cancer (long therapy required), rather than less profitable like infectious ones (fast and efficient treatment required) or orphan diseases (that affect only small numbers of individuals, usually genetic chronic dieases).

Efforts have been made to encourage companies to develop drugs for all kinds of diseases, provided by different mechanisms.

Other forms of exclusivity, than Intellectual Property Rights :
- simplification of marketing authorization procedures,
- **extended market exclusivity** (eg. The Orphan Drug Act, prevents similar product being **marketed);**
- data exclusivity / **protection** (available for all new drugs, protects against generic competition), regulatory data protection for new indications, etc.

Intellectual Property Rights**:**
- Patents (the best form of protection)**;**
- **Supplementary Protection Certificates** (extension of the duration of the rights conferred by patents; scope of protection limited by the patent and active ingredient/s of the authorized product, extension maximum +5 years; extra +6 months for pediatric extension available)

An innovator protects a drug candidate by various classes of patents:

- **product patents** (giving the broadest scope of protection;
- **method/s of obtaining a product**, sometimes „product by process";
- **first medical use** of a product (any medical use covered);
- **second medical use** for a different treatment / differnet indication;
- **second medical use** for a specific formulation, specific target group, selected patient populations, dosage regimen;
- synergistic effect while in composition with other compound

Do we need new medical use claims, especilly second medical use claims?

YES WE DO!

We want to be treated with new drugs, we want to cure incurable diseases, be treated more effectively, with a less expensive therapy, we want to live long and healthy….

Pharmaceutical companies would like to make money, thus must speed up the process and make it less expensive.

One of the ways is the strategy of drugs repurposing / retasking i.e.
to reinvestigate a drug candidate (which failed for a reason different than safety- non toxic) or a drug originally licensed for different disease for an activity for new therapeutic applications.

Why we need second medical use claims — drug repurposing and personalized medicine

Examples of a medicine first and second use which are not related

Medicine	First medical use	Subsequent medical use
Aspirin	Antipyretic/ Analgestic	Anti-stoke/ Anticoagulant
Amphotericin	Antifungal	Leshmaniasis
Gemcitabine	Antiviral	Anticancer
Raloxifene	Birth control	Osteoporosis treatment
Thalomid	Morning sickness	Anti-leprosy

(based on USFDA approvals, and Bhagwat et al., 2016)

The patent systems of most major countries (based on Article 27 of TRIPS, however with exclusions from patentability according to Articles 27(2) & 27(3), thus different legal standards for second medical use claims) provide for some sort of patent protection for new therapeutic uses for known active ingredients (new medical uses for existing medicines).

Comparison of the Polish Patent Law and the European Patent Convention

PL (Industrial Property Law):	EP (European Patent Convnention):
Patentable inventions- Art. 24 IPL Patents shall be granted – regardless of the field of technology – for **any inventions which are new, which involve an inventive step and which are susceptible of industrial application**.	Patentable inventions- Art. 52 (1) EPC European patents shall be granted for any inventions**, in all fields of technology, provided that they are new, involve an inventive step and are susceptible of industrial application.**
Exceptions to patentability- Art. 29 IPL Patents shall not be granted for: (iii) methods for treatment of the human or animal body by surgery or **therapy or diagnostic methods applied on human or animal bodies**; this provision s**hall not apply to products, and in particular to substances or compositions applied in diagnostics or treatment**.	Exceptions to patentability- Art. 53 EPC European patents **shall not be granted** in respect of: (c) methods for treatment of the human or animal body by surgery or **therapy and diagnostic methods practised on the human or animal body; this provision shall not apply to products, in particular substances or compositions, for use in any of these methods.**

Comparison of the Polish Patent Law and the European Patent Convention

PL (Industrial Property Law):	EP (European Patent Convnention):
Novelty - Art. 25 IPL **1. An invention shall be considered to be new if it does not form part of the state of the art**. 2. The state of the art shall be held to comprise everything made available to the public by means of a written or oral description, by use, displaying or disclosure in any other way, before the date according to which priority to obtain a patent is determined. 3. The content of any patent applications or utility model applications which enjoy the earlier priority, not made available to the public, shall also be considered as comprised in the state of the art, provided that they were published in the manner as specified in this Law. 4. The provisions of paragraphs (1) to (3) **shall not prevent a patent from being granted for a substance or compositions, comprised in the state of the art., for use or any specific use in the methods of treatment or diagnostics, as indicated in Art. 29 paragraph 1 point 3 provided that such use is not comprised in the state of the art.**	**Novelty - Art. 54 EPC** **1. An invention shall be considered to be new if it does not form part of the state of the art**. 2. The state of the art shall be held to comprise everything made available to the public by means of a written or oral description, by use, or in any other way, before the date of filing of the European patent application. 3. Additionally, the content of European patent applications as filed, the dates of filing of which are prior to the date referred to in paragraph 2 and which were published on or after that date, shall be considered as comprised in the state of the art. 4. **Paragraphs 2 and 3 shall not exclude the patentability of any substance or composition, comprised in the state of the art, for use in a method referred to in Article 53(c), provided that its use for any such method is not comprised in the state of the art.** 5. Paragraphs 2 and 3 shall also **not exclude the patentability of any substance or composition referred to in paragraph 4 for any specific use in a method referred to in Article 53(c), provided that such use is not comprised in the state of the art.**

Different ways of protecting a medical use

Different types of claims for protecting a medical use		
Type	**Way of drafting**	**Basis**
Method Of Treatment	**A method of treating disease Y** comprising administrating substance **X**. (US style method claims)	**USPTO allows claims in classic MOT format / not allowable in PL / EPO**
Swiss-type	**Use of** substance **X in the manufacturing** of the medicament for the treatment of disease ***Y***	Used to be allowable in PL and EPO (G5/83), (based on legal advice of the Swiss patent office 1984) adopted by national offices and EPO, not allowable after G 2|08
German/Canadian type use claims (Bare use claim)	**Use of** substance **X for** the treatment of disease **Y**	Not allowable in PL/ EPO – method of treatment (53(c) EPC),
Purpose limited product claim format (Product – for-use EPC2000)	Substance **X for use** in the treatment of disease **Y**	Purpose-limited product claim allowable in PL/ EPO, replaces Swiss-type claim format (EBA G2|08)

Source: Bhagwat et al., 2016 , AIPPI 2014 report

Coexistence of Swiss-type claims and purpose-limited product claims for many years to come

Practice in selected jurisdictions

Relevant national/regional offices for second medical use patents	
Type	**Permissible**
Method of medical treatment	Australia, **US** (*only permissible claim format in the US*)
Swiss-type	Australia, Austria, Belgium, Brazil, Bulgaria, Canada, China, Czech Republic, Denmark, Finland, France, Greece, Germany, Hungary, Ireland, Israel, Italy, Japan, Latvia, Mexico, Netherlands, New Zealand, Philippines, Russia, Singapore, Spain, South Africa, Sweden, Switzerland, Turkey, UK
Bare use claim	Australia, Austria, Brazil, Bulgaria, Canada, China, Czech Republic, Denmark, Finland, France, Greece, Germany, Hungary, Israel, Italy, Japan, Latvia, Mexico, Netherlands, Philippines, Russia, Singapore, Spain, Sweden, Switzerland, Turkey
Purpose limited product claim format (Product for use EPC2000)	Austria, Belgium, Bulgaria, Canada, Czech Republic, Denmark, Finland, France, Greece, Germany, Hungary, Ireland, Israel, Italy, Japan, Latvia, Mexico, Netherlands, **Poland,** Portugal, Russia, Spain, Sweden, Switzerland, Turkey, UK, **EPO**

Source: Bhagwat et al., 2016 , AIPPI 2014 report

Countries which DO NOT provide second medical use patent protection
Argentina, Dominican Republic, Egypt, **India**, Paraguay, Venezuela, Uruguay

Source: Bhagwat et al., 2016 , AIPPI 2014 report, up-to-date as for 2016

Art. 53(c) EPC surgery, therapy & diagnostic methods vs. Art. 54 EPC (4) (5)

First and second or further medical use of a known substance - exception from the general principle that product claims can only be obtained for absolutely novel products.

Non-patentable:

- A method for treating **Y** (cancer) which comprises administering an effective amount of substance **X**
- Use of an effective amount of substance **X** as a **medicament**/ for treating Y

Patentable (1st medical use) :

- **Substance X** (in vitro differentiated stem cells) **for use** as a **medicament.**

(even if X is a known product, but its use in medicine is not known)

- **Substance X** (composition comprising X) **for use** in the treatment of **Y** (cancer).
- Composition **for use** in the therapy of **Y** comprising **X** / Composition comprising **X for use** in the therapy of **Y**

Patentable (2nd medical use):

- **Substance X** **for use** in the treatment (therapy/ method of treating/ method of therapy) of Z / epilepsy (as a anti-infalmatory medicament - *medicament defined by its function*).

*(even if substance X is known as a medicament in prior art, or a medicament for a different disease, provided that such claim is inventive, the presence of **„ for use"** is mandatory* GL G VI-6 7.1.2 *).* This principle applies only to substances and compositions and cannot be extended to other products.

A claim directed to the further therapeutic use of a substance/ composition should indicate the illness/disease to be treated, the nature of the therapeutic compound used for that purpose and, if relevant for establishing novelty and inventive step, the subject to be treated. If the further therapeutic use relates to a different therapy of the same disease using the same substance/composition, the claim should also define all technical features of the therapy giving rise to the desired technical effect (G 2/08).GL G VI-6 7.1.2

- Substance X **for use** in the treatment (therapy/ method of treating/ method of therapy) of Z, **wherein** substance X is /administered topically / three times daily in the dose…./ is in the form of a nanoprarticle….

P.414021- easy case

Doxorubicin antibiotic from the anthracycline group known as an anticancer agent.
Antioxidant and detoxification properties are also demonstrated by isothiocyanates, as well as usefulness of isothiocyanates in reducing the side effects of doxorubicin.
The use of micelles and liposomes as drug carriers, including anticancer drugs also was known in the art.

Unexpectedly, an increased anti-tumor activity has been found for liposomes containing a mixture of doxorubicin and isothiocyanates (isothiocyanates increased the toxicity of doxorubicin in cancer cells, the synergistic effect of doxorubicin and isothiocyanates has been shown)

GRANTED:

Claim 1 (as filed- no office action).

A pharmaceutical formulation with antitumor properties comprising **doxorubicin** and at least one **isothiocyanate** as a substance that enhances the effect of doxorubicin **for use** in the treatment of **cancer**, **wherein** doxorubicin and at least one isothiocyanate are placed in a **lipid carrier**.

Why:
- good comparison examples, different types of cancer models, synergistic effect shown, no suggestions in prior art

P.399962 - complicated case

Novel use of oleacein (especially obtained from Ligustum Vulgare L.,in the manufacturing of a preparation stabilizing atherosclerotic plaque. Such a preparation may be used in particular in the prevention and treatment of diseases caused by the degradation of atherosclerotic plaque, most specifically ischaemic stroke, myocardial infarction and ischaemic heart disease

Claim 1. PL/ EP/PCT as filed

The use of oleacein for manufacturing a product for treatment or prevention of diseases resulting from atherosclerotic plaque rupture, particularly those selected from the group including: ischaemic stroke, myocardial infarction and ischaemic heart disease. (*Swiss type claim, which was later in EP changed into purpose limited product claim*)

Claim EP as granted (PL similar scope granted):

1. **Oleacein obtained from *Ligustrum vulgare L.* for the use in** atherosclerotic plaque stabilisation or **for use** in reduction of atherosclerotic plaque inflammation, especially in the treatment and prevention of diseases resulting from atherosclerotic plaque rupture, particularly those selected from the group including: ischaemic stroke, myocardial infarction and ischaemic heart disease, **wherein oleacine is obtained by the process as follows**,

- 400g of raw material **privet leaves** are extracted four times with distilled water at a temperature of 30ºC in an ultrasound bath, for 30 minutes each time at a ratio of 1:10 raw material to solvent;
- the aqueous extract is filtered through wool;
- the resulting aqeous extract is concentrated through lyophilisation to volume of 1 liter;
- the condensed aqueous extract is subjected to 5-fold diethyl ether extraction at ratio of 1:1 solvent on rotary evaporator under reduced pressure, at temperature of 35ºC to obtain about 5g of diethyl ether extract;
- the diethyl ether extract is separated using flash chromatography in a coulmn filed with silica gel using as isocratic system of chloroform and ethyl acetate (85:15) for 60 minutes at 20ml/min., obtaining 9 fractions, from which fractions 3 and 4 are selected for subsequent separation;
- said fraction 3 and 4 further separated on a column filed with silica gel using an isocratic system of toluene, methyl acetate and methanol (84:11:5) for 60 minutes at 20/min, obtaining 5 fractions;
- from fraction 3, loaded onto a column filed with sephadex, **oleacein is isolated** using a mixture of chlorophorm and methanol (9:1).

Cases from our practice and tips for Polish applicants

Claim 1. as filed in US

A method for treatment or prevention of a disease resulting from atherosclerotic plaque rupture, said method comprising administering oleacein to said patient

Claim 1. as granted in US

1. A method for inhibiting MMP-9 production by atherosclerotic plaque cells in a patient, said method comprising administering oleacein to said patient, wherein said oleacein is obtained from *Ligustrum vulgare L*

Why (so different scope of protection):

- oleacein was known as the compound;

- oleacein was known as possessing antioxidant activity;

- different national regulations, US one year „grace period";

- the abstract has been published on a conference with earlier date that the priority date , which indicated the **medical use of oleacein in the cardiovascular prevention indicated:** information in the abstract: **oleacein (from virgin olive oil)** may contribute to stabilization of atherosclerotic plaques: oleacein contributes to stabilization of atherosclerotic plagues by decrease of myeloperoxidase release from neutrophils, which **may explain the role of olive oil in cardiovascular prevention**);

- the discovery of alternative **mechanism** of action does not add an improved technical effect to well-known medical uses / the resulting technical effect remains the same;

- limitation of the claim to use - **oleacein obtained from *Ligustrum vulgare L.* for the use in medical treatment wherein oleacein is obtained by the process as described in the application +** additional examples confirming that the final product obtained by this process (aqueous extractions) is different than the product from the prior art (oleacein form olive oil), and that additional effect is obtained by such product (higher purity and activity and thus improved effect observed)

Tips for the Polish applicants

Suggestions for patent drafting for applicants for cases relating to medical / furter medical use:

- Prepare the strategy with your client; check the prior art (ask your client for any disclosures), prepare for fallback scenario;
- Provide a clear difference between the invention and prior art and effect associated, and show that you solved a specific technical problem;
- Provide as many examples as possible; provide comparative examples;
- A further therapeutic use of a substance/ composition should indicate the illness/disease to be treated, the nature of the therapeutic compound used for that purpose and, if relevant for establishing novelty and inventive step, the subject to be treated;
- If the further therapeutic use relates to a different therapy of the same disease using the same substance/composition, the claim should also define all technical features of the therapy giving rise to the desired technical effect;
- Think about different jurisdictions your client may enter in the future, prepare for filing of different sets of claims and different requirements involved (e.g. describe a method of treatment in the description).

And the final note:

The problem with scope of protection and possible infringement of the second medical use claim !

Thank you for your attention!

Questions?

www.wtspatent.pl

In the presentation the information / materials./ data from the following were used
EPO web page, PPO web page and articele Bhagwat at al. Second Medical Use Patenting Across Different Jurisdictions , Jurnal of IPR, vol.21 July 2016

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