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Learning path for patent examiners

Assessment of novelty: chemical inventions: Advanced level

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Introduction

This publication, "Assessment of novelty: chemical inventions, Advanced level", is part of the "Learning path for patent examiners" series edited and published by the European Patent Academy. The series is intended for patent examiners at national patent offices who are taking part in training organised by the European Patent Office (EPO). It is also freely available to the public for independent learning.

Topics covered include novelty, inventive step, clarity, unity of invention, sufficiency of disclosure, amendments and search. Also addressed are patenting issues specific to certain technical fields:

- patentability exceptions and exclusions in biotechnology
- assessment of novelty, inventive step, clarity, sufficiency of disclosure and unity of invention for chemical inventions
- the patentability of computer-implemented inventions, business methods, game rules, mathematics and its applications, presentations of information, graphical user interfaces and programs for computers
- claim formulation for computer-implemented inventions

Each publication focuses on one topic at entry, intermediate or advanced level. The explanations and examples are based on the European Patent Convention, the Guidelines for Examination in the EPO and selected decisions of the EPO's boards of appeal. References are made to the Patent Cooperation Treaty and its Regulations whenever appropriate.

The series will be revised annually to ensure it remains up to date.

Disclaimer

All references to natural persons are to be understood as applying to all genders.

Contents

Legal references

1. Learning objectives

Participants to this course will learn:

- The principle of novelty assessment for polymorphic- / isotopic-forms and antibodies
- The fundamentals of prior use of drugs in development and clinical trials
- To understand dosage regimen and new clinical situations in second medical use claims

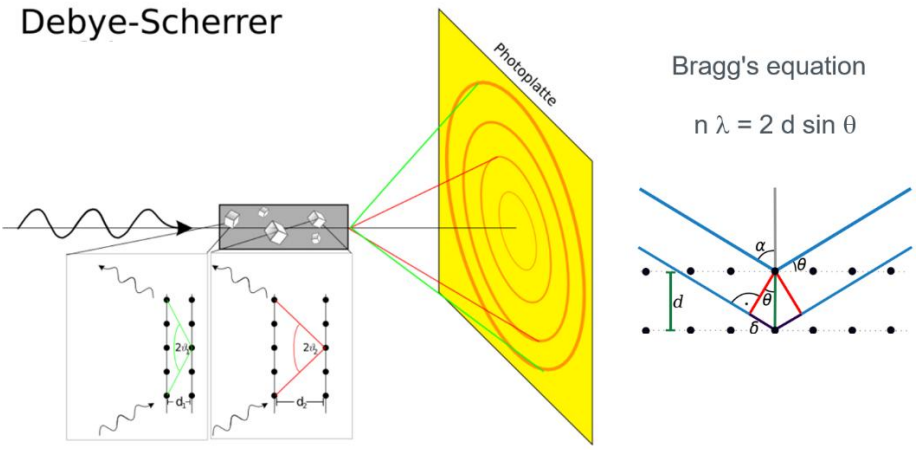
2. Novelty of polymorphic forms

A chemical substance is considered **novel** if it **differs** from a known substance **on account of a reliable parameter** (T 296/87). The solid-state appearance may be one such parameter.

Chemical substances can appear in more than one solid-state form. These forms can have different appearances (e.g. crystallise differently), different physical properties (e.g. melting points) and different physiological properties (e.g. dissolution rate, stability *in vivo*).

A chemical compound therefore may be novel over another that has the same molecular formula and the same chemical structure but appears in a different solid-state form (e.g. different crystal structure – amorphous vs. crystalline).

In order to characterise a solid-state form, the substances are analysed by X-ray powder diffraction ("XRPD") in accordance with the Debye-Scherrer method and the diffraction peaks are recorded. The X-rays are diffracted along the atom planes within the crystal lattice. The atom plane distances "d" characterise the solid-state form. According to Bragg's law, they correlate with the maxima of the diffracted rays (2-theta values).



The list of 2-theta values is considered to characterise the material sufficiently. As this is a parameter-in-a-claim construction, the claim must include the measurement method.

It may be that the prior art has not characterised the solid-state form by XRPD. An objection for lack of novelty may be raised as a result, particularly if other physical parameters (such as melting points) are identical or very similar in the claimed polymorph and the prior-art solid-state form.

An objection of insufficiency of disclosure may be raised if the measurement method has not been sufficiently disclosed (particularly the wavelength of the X-ray source) or if the method of obtaining the disclosed solid-state form does not make it possible to reliably obtain the claimed material.

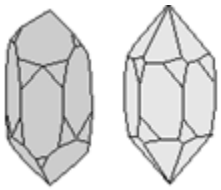
As it is not unusual for organic compounds to exist in a number of solid-state forms, identifying a novel solid-state form does **not automatically** render the related claims **inventive**. Instead, showing an unexpected technical property of a new solid-state form is also a requirement for patentability.

It is common general knowledge that e.g. a crystalline form is thermodynamically more stable than an amorphous form, and that e.g. an amorphous form has a higher dissolution rate than a crystalline form. These are examples of technical effects that are **not unexpected**.

The method for reliably obtaining the polymorph must be sufficiently disclosed. Disclosure that the new polymorph is obtained from seeding crystals is considered insufficient as the seeding crystals only become available once the polymorph has been obtained.

Examples

The image below shows polymorphous quartz crystals. They represent the same substance and have the same formula but appear in two different physical forms. They behave differently (e.g. with regard to diffractive index, diffraction of X-rays).



Example of a polymorph claim:

"Crystalline form of compound X, characterised by main peaks in its powder X-ray diffraction pattern obtained using copper K-alpha1 radiation at 9.0, 14.2, 23.9 and 27.1 ± 0.2 degree 2-theta."

Legal references:

Art. 54 EPC, Art. 83 EPC, Art. 56 EPC, CL Book I.D.9.8, T 777/08

3. Novelty of isotopic forms

A chemical compound may be novel over another that has the same molecular formula and stereospecificity but a different isotopic composition.

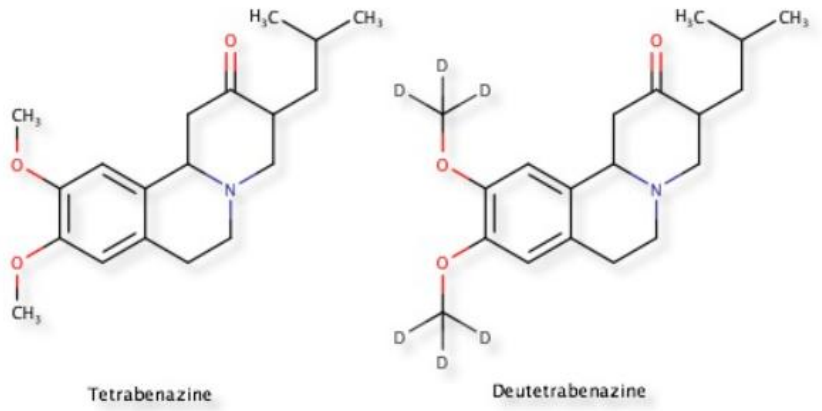
The most frequently used elements for isotopically labelling compounds are ^{18}F, ^{2}H (i.e. deuterium, written often as "D"), ^{11}C and ^{13}N. Of these,^{18}F and ^{2}H are by far the most frequently used.

^{18}F-radioisotopically labelled compounds are used in PET (positron emission tomography, an *in vivo* imaging technique). The travelling and fate of these labelled compounds as they pass through the human body can be detected by a PET scanner and can give valuable insight into the ADME properties of drugs or the state of diseases (cancer, Alzheimer's) without any surgical intervention on the body.

The positron-emitting isotope administered to the patient undergoes β^+ decay in the body, with a proton being converted to a neutron, a positron (the antiparticle of the electron, sometimes referred to as a β^+ particle) and a neutrino. The positron travels a short distance and annihilates with an electron. The annihilation reaction results in the formation of two high-energy photons which travel

in diametrically opposite directions and pass through (human) tissue. Two detectors facing each other detect these photons and their place of origin in the tissue can be computed to give a picture of the tissue.

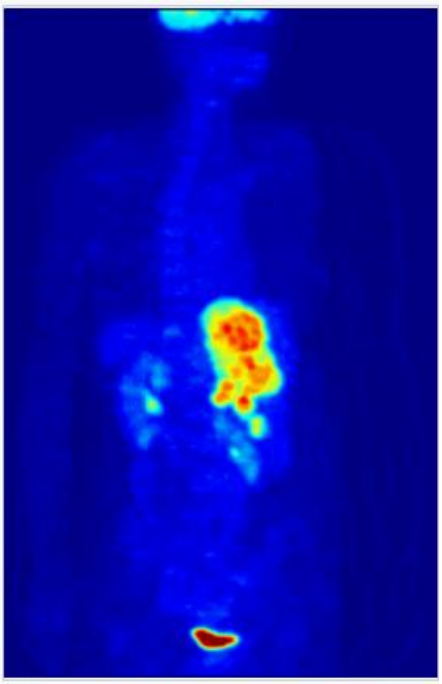
Deuterated drugs behave differently compared with their hydrogen counterparts. Deuterating drugs at metabolic attack sites can increase their metabolic stability. The corresponding drugs are novel over the conventional drug.



Deutetrabenazine is an FDA-approved drug.

Examples

^{18}F-fluorodeoxyglycose (^{18}F-FDG) is a radiopharmaceutical used for PET imaging. It is a marker for glucose, and so will accumulate in tissue with high metabolic turnover (such as in tumours).



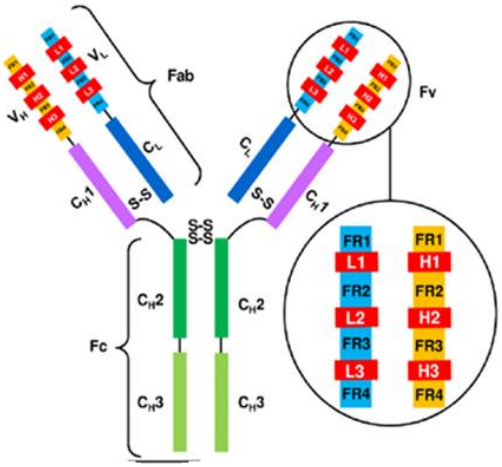
Whole-body PET scan using ^{18}F-FDG to show liver metastases of a colorectal tumor

^{18}F-FDG is novel over fluorodeoxyglycose.

Legal references:
Art. 54 EPC

4. Novelty assessment of antibodies: definitions

Conventional antibodies are large, Y-shaped proteins naturally produced by plasma B-cells and composed of two identical light chains and two identical heavy chains, both containing variable and constant domains. Antibodies bind specifically to antigen targets via the antigen-binding region, which contains complementarity-determining regions (CDRs). Normally the six CDRs form the site which interacts with the antigen (paratope). The CDRs are highly variable and are positioned by the framework region (FR).



In addition, heavy-chain-only antibodies have also been described. They are originally found in camelids and sharks, and consist of only two identical heavy chains (with variable and constant domains) and the antigen-binding region consists of a single variable domain with three CDRs.

Various approaches have been developed to provide antibodies. Antibodies can be produced by immunisation of animals followed by fusion of antibody-producing cells with myeloma cells, resulting in hybridoma cells. In vitro approaches are mainly based on screening antibody libraries displayed by phage, yeast, mammalian cells, and/or ribosomes. Human antibodies are of particular interest and can be produced in transgenic animals expressing human immunoglobulin loci, or by retrieving antibody-producing cells from human subjects. As of recently, it is also possible to employ AI tools to generate new antibodies.

Knowledge of the structure-function relationships of antibodies makes it possible to provide a number of derivatives for a multitude of applications. Variants of antibodies, antibody fragments, bispecific or multi-specific antibodies and antibody fusion products are commonly designed and produced.

In general, antibodies, i.e. conventional antibodies, recombinant antibody derivatives or new antibody formats, can be defined by one or more of the following:

- their own structure (amino acid sequences)
- nucleic acid sequences encoding the antibody
- reference to the target antigen
- target antigen and further functional features
- functional and structural features
- production process
- hybridoma producing the antibody

An antibody can **be defined by the antigen it binds to**, as long as the antigen is clearly defined in the claims. The novelty of a claim reading "An antibody Y that binds to antigen X" depends on the prior art as follows:

- In T 0582/95, the board ruled that, if the antigen X was unknown and the antibodies against X were also unknown, novelty could be acknowledged.
- If the antigen is known but the prior art is silent about antibodies against it, the claimed subject-matter is novel. If antigen X is known and the claimed antibody Y against X is also known, the claimed subject-matter is not novel. However, the use of the antibody can be novel and inventive, for example: "Monoclonal antibody Y for use in treating disease X."
- An antibody can also be defined by its ability to bind to a well-defined antigen in combination with a negative feature, for example: "Antibody binding to antigen X and not binding to antigen Y".

Claim wording related to an antigen-defined antibody is accepted but does not exclude known antibodies raised against other known antigens. Examples of such wording:

- antibody binding to X
- anti-X antibody
- antibody reacting with X
- antibody specific for antigen X
- antibody binding to antigen X consisting of the sequence defined by SEQ ID NO:xxx

Novelty cannot be acknowledged merely because the antigen is unknown. The claims should state that the binding is specific to the corresponding antigen.

In the context of T 1902/11, the board used a prior-art document in which a 100-fold increase in affinity was considered to be specific, further stating that the skilled person would know when a binding was "specific".

The description may provide another definition of "specific" which needs to be taken into consideration.

Adding a negative limitation – "An antibody that specifically binds to antigen X and does not bind to antigen Y" – is allowable but it must be clear.

Antibodies defined by **structural features** – if the sequences considered to be essential for binding are correctly disclosed in the description (Rule 30 EPC) and unknown in the prior art, the claims are novel.

Examples

Antibodies defined by **antigen specificity** and **structural features**

Example 1:

"Monoclonal antibody binding to X comprising a heavy-chain variable domain of SEQ ID NO:1 and a light-chain variable domain of SEQ ID NO:2."

Example 2:

"A single-chain antibody binding to X comprising VH CDR1, CDR2 and CDR3 consisting of the amino acid sequence of SEQ ID NO:1, 2 and 3, respectively, and VL CDR1, CDR2 and CDR3 consisting of the amino acid sequence of SEQ ID NO:4, 5 and 6, respectively."

If the sequences are novel over the prior art, the claims are novel.

Legal references:
Art. 54 EPC

5. Public prior use of drugs in development and clinical trials

Imagine the following example for public prior use. A tablet is marketed by company X and the available prior art discloses the ingredients but not their amounts. Company Y files a patent application with the same ingredients, but the application discloses specific amounts. Is the marketed tablet relevant as prior art for novelty/inventive step?

G 1/92 provides an answer:

"The chemical composition of a product is state of the art when the product as such is available to the public and **can be analysed and reproduced** by the skilled person, **irrespective of whether or not particular reasons** can be identified for analysing the composition."

Depending on the level of disclosure, it might be difficult for said analysis to meet the requirements of the novelty/inventive-step assessment.

Patients participating in clinical trials are usually not bound to secrecy as they are allowed to discuss details of their treatment with family members or their family doctor. Patient consent forms are not generally publicly available either.

In most cases, however, the participants do not know the exact details of the study or whether they are in the placebo or verum group.

Furthermore, any person involved in a medical process (medical personnel) is obliged to maintain confidentiality given the need for patient privacy and the need to protect the development and testing of medical treatments and procedures.

As a result of these **various confidentiality measures**, a public prior use is not often cited against novelty during the examination procedure, usually being relevant during post-grant proceedings instead.

Clinical trials may also be started before a patent is filed, particularly when a patent application is claiming a medical use and a clinical trial to analyse that use has been published before the application's priority/filing date. Under Article 54(2) EPC, an objection of lack of novelty requires that the claimed invention be "made available to the public".

So, in order to be novelty-destroying prior art, a document must:

- clearly disclose the essential conceptual features of the medical use, i.e. the substance/composition used for treating the medical indication and any essential features of the treatment (**enabling disclosure**)
- render the underlying therapeutic **effect plausible** (it is, however, not necessary to explain the mechanism underlying the effect as long as the claimed therapy is plausibly shown to have a therapeutic effect)

Hence, if a prior-art document discloses clinical trials such as phase I, II or III studies (or states that these investigations are ongoing) but fails to disclose any positive results of these studies or other plausible basis, such as pre-clinical tests, then that document is normally not considered novelty-destroying (T 158/96, T 715/03, T 385/07, T 1859/08, T 2506/12, T 239/16) since requirement (ii) would not be fulfilled.

That said, disclosure of fully detailed rigorous testing with statistical analysis is not required. Since clinical trials fail more often than they succeed, merely announcing a clinical trial may not be enough to make the claimed invention available to the public. Efficacy does not have to be shown for every treatment – success even for just part of the previously treated group is generally considered a valid anticipation (partial healing is also therapy: T 443/01, Reasons 3.3).

Example

An application was filed with the following claim relating to a dosage regimen:

"*Zoledronic acid… for use in a method of treating osteoporosis in which the zoledronic acid … is administered intravenously and intermittently and* ***in which the period between administrations is about one year***."

The most relevant prior-art document disclosed a multi-arm clinical study with five study arms for treating osteoporosis in humans, with one possible treatment being the treatment regimen as claimed, i.e. intravenous administration of zoledronate given once yearly. However, results of the study were not reported, so that an effective treatment of osteroporosis was not explicitly disclosed.

An effective treatment of osteoporosis could also not be regarded as implicitly disclosed, because zoledronic acid was known from further prior art to be effective in the treatment of osteoporosis in animals, but not in humans.

Consequently, the subject-matter of the claim in question was found to be novel.

Legal references:

G 1/92, T 158/96, T 715/03

6. Characterising features in second medical use claims: dosage regimen

A purpose-related product claim may also be patentable if a dosage regimen is the only feature claimed which is not part of the state of the art (T 1020/03 and G 2/08; confirmed by T 1319/04, T 826/06 and T 795/06).

The dosage regimen must not only be verbally different from what is described in the state of the art but must also **reflect a different technical teaching** in order to establish novelty (G 2/03, Reasons 6.3).

Often, determining appropriate dosages will be considered a matter of routine for the skilled person. Technical effects arising from the dosage regimen, such as improved therapeutic efficacy, will thus be key when examining inventive step.

For example, providing a new dosage regimen with reduced dosing (reducing the drug load on the patient) compared with the conventional treatment but providing equivalent therapeutic results (as evidenced in the application) has also been accepted as being inventive in some cases.

In T 1020/03, a pure dosage regimen was recognised as not being excluded from patentability for the first time. The claims were directed to the use of insulin-like growth factor-I in the preparation of a medicament to be administered to a mammal in a specific discontinuous administration pattern.

Legal references:
Art. 53(c) EPC, Art. 54(5) EPC, CL Book I.C.7.2.4, G 2/08, T 1020/03

7. Characterising features in second medical use claims: new clinical situation

A new mechanism of action or a new technical effect can yield a new clinical situation, which may be considered patentable under Article 54(5) EPC.

In T 836/01, the board accepted that claims directed to the use of IL-6 to directly influence tumour growth and differentiation were novel over a prior-art disclosure of the use of IL-6 to indirectly treat cancer by activating T-cells, finding that a new technical effect resided in the medical indication for **directly treating cancer** instead of **enhancing the immune system**.

Applying the principles of decision G 5/83, the board concluded that the technical effect relied upon in the claimed invention identified a **new clinical situation**. Since a new clinical situation was – as an abstract concept – inseparable from a patient suffering from it, the conclusion was that this new clinical situation also identified a new sub-group of subjects being treated.

Another example of a new clinical situation is T 1955/09, in which the board needed to decide whether the claimed use (compound X for use in treating a bacterial or fungal infection in a mammal by killing said bacteria or fungi) represented a further and different therapeutic use compared with the disclosure in document D1 (compound X may be used to neutralise toxins produced by bacteria or fungi). The board concluded that the technical effect relied upon by the claimed invention, i.e. the antibiotic effect, was **not** a mere explanation of how the compounds inhibited or neutralised toxins.

Instead, this effect identified **a new clinical situation**, namely one in which it could be preferable to target the infection itself rather than merely the toxins produced by the bacteria or fungi causing the infection.

Careful analysis is necessary to identify new clinical situations versus merely explaining the mechanism of action.

In T 384/03, the claims were directed to the use of carbonic anhydrase inhibitor (CAI) for treating glaucoma by **increasing ocular blood flow** (OBF). This was considered to be **not novel** over a prior-art disclosure of the same CAI for treating glaucoma **by lowering intraocular pressure** (IOP). Although a new effect (increased OBF to treat glaucoma) was discernible, it was "in the same direction" as the known effect (lowering IOP to treat glaucoma).

CAI → increases OBF → lowers IOP → treating glaucoma

Accordingly, the increased OBF **was the cause** of the known lower IOP mechanism (i.e. it was not independent from it), so there was no new clinical situation.

T 254/93 is another example in which the clinical situation was not considered new. The examining division refused an application relating to the use of a retinoid compound in association with the use of corticosteroids to prevent skin atrophy. Although it concerned a specific aspect of the known use, the use specified in claim 1 (prevention of skin atrophy) was not actually different from the known use in the prior art (treatment of dermatoses).

The board noted that when a second medical indication was claimed in relation to the use of a constituent in preparing a known composition and the final effect was apparent when using the known composition for the known purpose, there was no discernible technical problem in either obtaining the final effect or preparing the composition.

The only remaining question could have been the explanation of the phenomenon underlying the treatment according to the known process. However, **merely explaining an effect** obtained when using a compound in a known composition could not render a known process novel if the skilled person was already aware of the occurrence of the desired effect when applying the known process, even if the explanation related to a pharmaceutical effect which was not known to be due to that compound in the known composition.

Legal references:
Art. 53(c) EPC, Art. 54(5) EPC, CL Book I.C.7.2.4, T 836/01, T 384/03

8. Beyond the course

You can deepen what you have learned during this course with the following further readings:

Polymorphisms and Patent, Market, and Legal Battles: Cefdinir Case Study; Cabri et al; *Org. Process Res. Dev.* 2007, 11, 1, 64–72; Publication Date:December 20, 2006; https://doi.org/10.1021/op0601060

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