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European Biotech Case Law Webinar

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Speakers

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Agenda

- T 2218/16 (BEZZUBOVA)
- T 3035/19 (EURO-CELTIQUE et al.)
- T 2759/17 (Kao Corporation)
- T 1989/18 (HOFFMANN-LA ROCHE)
- A link to download these slides and a recording of this webinar will be emailed to you on Wednesday 09 February 2022.

T 2218/16 (Gene therapy of motor neuron disorders/BEZZUBOVA)

- Plausibility and gene therapy

Plausibility – concept

- The extent of the monopoly conferred by a patent should correspond to and be **justified by the technical contribution** to the art.
- Not essential for application to have experimental data or results, provided that nature of invention relies on a technical effect which is self-evident/predictable/based on conclusive theoretical concept, i.e. **plausible**.
- Originates in EPO case law as response to overly-broad claims and to **prevent speculative claims** i.e. “armchair inventors”.
- Can arise in context of **sufficiency or inventive step**.

Plausibility – sufficiency (Art. 83 EPC)

- Arises when technical effect is a feature of the claims.
- Experimental results are not always required in the application to establish sufficiency, in particular if the application discloses a **plausible technical concept** and there are **no substantiated doubts** that the claimed concept can be put into practice.
- The application may provide **suitable evidence** for the claimed therapeutic effect; or

  it may be **derivable** from the prior art or common general knowledge.

Plausibility – inventive step (Art. 56 EPC)

- Arises when technical effect is relied on for demonstrating an inventive step (e.g. an unexpected advantage).
- There can only be an invention if the application makes it at least **plausible** that its teaching indeed solves the problem it purports to solve.
- “Absolute proof” may not required for the effect to be “plausible”.

Summary of established case law

- **Experimental data is not always required** if effect is derivable from the prior art or common general knowledge.
- Application must disclose a **plausible technical concept** (“ab initio plausibility”).
- There must be **no substantiated doubts** (“ab initio implausibility”).
- Further case law:
  - Context of sufficiency (e.g. CLBA II.C.7.2)
  - Context of inventive step (e.g. CLBA I.D.4.6)
  - Post-published documents (e.g. CLBA II.C.6.8 and CLBA I.D.4.6).

T 2218/16: background

- Claim 1: An AAV9 vector comprising a therapeutic gene for use in a method for treating a motor neuron disorder.
- Claim 5: the disorder is selected from neurodegenerative diseases, neuromuscular diseases, pain, lysosomal diseases, trauma, bone marrow injuries, cancers of the nervous system, demyelinating diseases, autoimmune diseases of the nervous system, neurotoxic syndromes, sleeping disorders.
- The application provided data that **AAV9 surprisingly infected spinal cord motor neurons** in animal models.

T 2218/16: background

"1. An AAV vector comprising a therapeutic gene for use in a method **for treating a motor neuron disorder** in a subject, wherein said AAV vector is administered by intraperitoneal (i.p.), intramuscular (i.m.) or intravenous (i.v.) injection, preferably intravenous injection, to said subject, said **administration causing infection of spinal cord motor neurons and expression of the gene in spinal cord motor neurons**, wherein said AAV vector is:

- a double-stranded **self-complementary AAV9 vector**, or
- **a pseudotyped AAV vector** comprising a double-stranded **self-complementary** AAV genome derived from an AAV serotype different from the AAV9 serotype and a **capsid derived from an AAV9 capsid**; and

wherein the therapeutic gene is operably linked to a promoter specific or functional in motor neurons".

T 2218/16: opponent's arguments

Suitability of AAV9 vectors for the claimed therapeutic applications was **not plausible**:

- Some of the disorders in dependent claim 5 were **unrelated to motor neuron disorders**, for example, cancer and sleeping disorders. The suitability of AAV9 vectors for the treatment of certain diseases, such as SMA, could not be generalised to all diseases covered by claim 1.
- The patent neither disclosed a **mechanism** by which the AAV9 vectors achieved a therapeutic effect, nor a **causal link** between spinal cord motor neurons and the diseases cited in claim 5.
- The patent did not disclose the suitability of the claimed AAV9 vectors when **administered intraperitoneally (i.p.), or intra muscularly (i.m.)**.
- The patent was silent on using any other viral genome than that of **AAV2** for attaining a therapeutic effect.

T 2218/16: Board’s decision

- The provision of evidence in the patent application for a claimed effect is not a prerequisite for patentability, if, based on the data in the patent application/patent, or from common general knowledge, it is **plausible** that a product (here scAAV9) is suitable for the claimed therapeutic applications.
- A successful objection of lack of sufficiency of disclosure presupposes that there are **serious doubts**, substantiated by verifiable facts that the skilled person is not able to carry out the invention as claimed without undue burden.

T 2218/16: Board's decision

- The **burden of proof** as a general rule is upon an opponent to establish, on the balance of probabilities, that a skilled person reading the patent, and using common general knowledge, would be unable to carry out the invention.
- The burden of proof can be reversed, however, in limited circumstances. When the patent does not contain detailed information, a weak presumption exists and the opponent can discharge its burden by **plausibly** arguing that common general knowledge would not enable the skilled person to put this feature into practice.
- The weight of arguments and evidence required to rebut this presumption depends on its strength.

T 2218/16: Board's decision

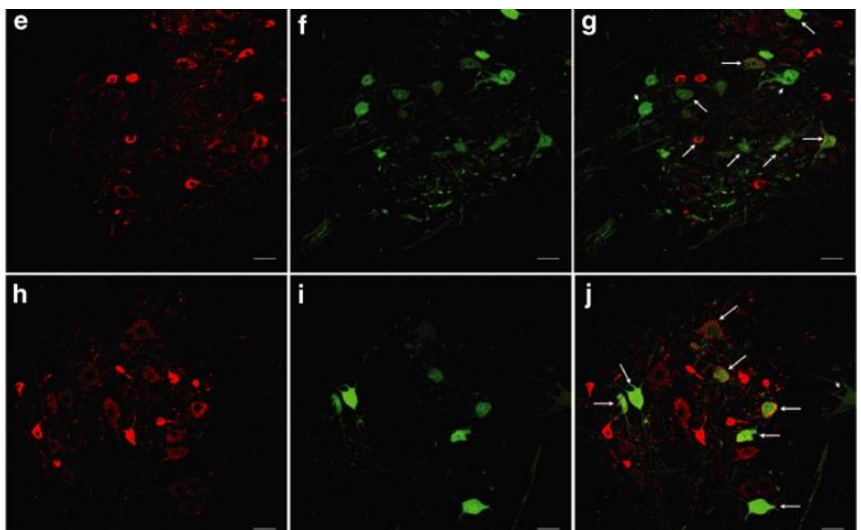
- It is uncontested that the patent provides sufficient information about the **general availability** of the scAAV9 vector, including its production.
- The **working examples** in the patent further demonstrate that an i.v., i.m., or i.p. administered scAAV9 vector in mice and cats delivers and expresses a reporter gene in spinal cord motor neuron:
  - Example 3: Transgene expression in **cells with a motor neuron-like phenotype** after i.m. or i.p. injection of scAAV9-GFP in the neonatal mouse
  - Example 4: Transgene expression in the CNS after i.v. injection of scAAV9-GFP or ssAAV9-GFP in the neonatal mouse
  - Example 6: Transgene expression in the spinal cord after i.v. injection of scAAV9-GFP in LIX-1 kittens

T 2218/16: figure 10*

*Corresponding figures reproduced from related publication (Duque, S., et al., 2009. Molecular Therapy, 17(7), pp.1187-1196) for clarity. Original figures were low quality images in black and white.

GFP immunocytochemistry

(**e–j**) Double-labeled transverse sections of the spinal cord of both affected (**e–g**) and non-affected (**h–j**) kitten, treated for ChAT* immunofluorescence (**e,h,** red) and GFP native fluorescence (**f,i**, green). (**g,j**) Merge (arrows: transduced MNs). Bars = (**a**) 200 µm; (**b,c**) 100 µm; (**d–j**) 50 µm.



*Motor neurons express choline acetyltransferase (ChAT)

T 2218/16: Board’s decision

- Since the scAAV9-mediated delivery and expression of a reporter gene and of a therapeutic gene to spinal cord motor neurons are based on the **same mechanisms**, the Board is satisfied that the patent discloses a concept which is generally suitable for the delivery of therapeutic genes to spinal cord motor neurons.

T 2218/16: Board’s decision

- Consequently, the Board considers that the overall technical teaching provided in the patent - **far from being a mere statement** - amounts to a strong presumption of suitability, so that in the present situation the appellant carries the burden of proof.
- Moreover, since the appellant's submissions on insufficiency are not supported by evidence, i.e. verifiable facts, the burden of proof is not shifted to the respondents. Thus, **in the absence of any evidence to the contrary**, the Board decides that the main request complies with Article 83 EPC.
- Although did not comment on whether all the therapies in claim 5 could be treated, it appears that the **burden was on the opponents** to substantiate the doubts: “*The Board also does not disregard that the subject-matter claimed in claims 1 and 5 is broad. Nevertheless this is not per se a sufficient reason for discharging the actual burden on proving insufficiency*.”

T 2218/16: novelty

- D2 discloses the same scAAV9 vector, therapeutic genes, motor neuron disorders to be treated, mode of administration.
- D2 discloses GFP expression in various brain cells, including neuronal cells in the "*enthorhinal cortex*",
- D2 disclosed: "…a strong GFP expression was also found in fibres of the corticospinal tract … Transduction of these fibres likely results from infection of upper motor neurons…"
- Board found that **D2 does not directly and unambiguously disclose that motor neurons are transfected**, since the term "likely" implies a probability only that the transfected cells are indeed motor neurons.
- According to established case law, subject-matter is directly and unambiguously derivable from a prior art document only, if it is "beyond doubt - not merely probable".

T 2218/16: novelty

- Opponent argued that infection of spinal cord motor neurons had to be achieved by the remaining features of the claim, all of which were disclosed in document D2.
- Therefore document D2 ***inherently*** disclosed the "result-to- be-achieved" feature. This case resembled previous decisions which denied novelty of a second medical use claim, because a new technical effect alone did not result in a new clinical situation.
- Board disagreed – The alleged "result-to-be-achieved" feature in claim 1 relates to a **new technical effect**.

T 2218/16: novelty

- Effect in D2 results from the transfection of cerebrospinal fluid (CSF) secreting cells whereby the therapeutic product is secreted into the CSF, where it acts from the external, i.e. indirectly, on disease-causing cells.
- Thus, document D2 teaches an **indirect** therapeutic effect on motor neurons.
- This is different from the technical effect relied upon in claim 1, i.e. the **direct** transfection of motor neurons.
- This in the Board's opinion, allows for the treatment of a new subgroup of patients, namely of a patient group that can no longer be treated by the extracellular approach disclosed in document D2, and hence, identifies a **new clinical situation** (see T 836/01, reasons 8).

T 2218/16: lessons

- Plausibility case law will apply to gene therapy applications:
  1. Does the application disclose a **plausible technical concept**?
  2. Are there **substantiated doubts** that the claimed concept can be put into practice?
- An inherent disclosure does not necessarily equate to a novelty destroying disclosure.
- Novelty can be acknowledged for a new mechanism of action if it creates a new clinical situation.

T 3035/19 (EURO-CELTIQUE et al.)

- Added Matter – pointer required for a selection from two lists

Background

- Appeal from Opposition Division decision revoking EP2425821.
- Claim 1 added subject matter (Art. 76(1) and 123(2) EPC).

Background

Article 123(2) EPC

- The European patent application or European patent may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed.

Article 76(1) EPC

- A European divisional application […] may be filed only in respect of subject-matter which does not extend beyond the content of the earlier application as filed […]

Background – the “gold standard” – G2/10

- “Any amendment […] can therefore, irrespective of the context of the amendment made, only be made within the limits of what a skilled person would derive directly and unambiguously, using common general knowledge, and seen objectively and relative to the date of filing, from the whole of these documents as filed”

Background – selection from lists – T727/00

- A combination – unsupported in the application as filed – of one item from each of two lists of features meant that although the application might conceptually comprise the claimed subject-matter, it did not disclose it in that particular individual form.

Claim 1 on appeal

"Pharmaceutical oral preparations for use in treating pain and for use in concurrently reducing opioid induced obstipation (OIP),

wherein each preparation comprises as the actives oxycodone…. and naloxone…

wherein oxycodone…is present in said preparations…in a ratio of 2:1 to naloxone".

Disclosure of application

- Application discloses several oxycodone:naloxone ratios, including the ratio of 2:1, and lists several side effects, one of which is OIC.

Decision – ratio of 2:1

- Ratio of 2:1 is disclosed as 1 of 7 particularly preferred ratios and is also exemplified.
- However, other ratios are also disclosed in these passages.
- No preference for 2:1 over the other exemplified or listed ratios.

Decision – OIC

- As to the feature relating to the reduction of OIC, the earlier application discloses that preparations according to the invention treat pain and that, at the same time, "common side effects such as obstipation, breath depression and development of addiction are suppressed”.
- The application as filed does not point to the choice of OIC over the other side-effects.
- According to the patentee, the skilled reader **equipped with common general knowledge** would understand the application as being first and foremost about reducing OIC when treating pain. Out of the opioid-induced side-effects mentioned in the application, OIC would be highly distressing and the most prevalent in real-world clinical practice, whereas the other side-effects mentioned were much less of a concern.

Decision – OIC

- Board held that the argument of the appellants amounts to inferring from common general knowledge a pointer to this particular selection in the absence of any justification therefor in the content of the earlier application as filed.
- A **reference to common general knowledge cannot compensate for the lack of disclosure** in the application itself.

T 2759/17 (Kao Corporation)

- Inventive Step - determining the closest prior art

Background

- EP2009993 relates to the use of a composition for supressing biofilm formation and removing an already-formed biofilm.
- Appeal: claims corresponding to AR1 of opposition.

Claim 1 on appeal

1. Use of a composition for suppressing biofilm formation and removing an already-formed biofilm the composition comprising the following component (A) and component (B):

(A) one or more compounds represented by the general formula (1):

[F1]

R^1O-(EO)p-H

wherein R^1 represents a linear or branched alkyl group or alkenyl group having 8 to 14 carbon atoms; EO represents an ethyleneoxy group; p represents an integer of 0 to 3 and

(B) one or more enzymes selected from the group consisting of hydrase and lyase.

Prior Art – E1

- Disclosed detergent compositions comprising:

  (a) a C12-15 predominantly linear primary alcohol condensed with ethylene oxide – falls within (A) of claim.

  (b) Hexosaminidase – falls within (B) of claim.

- The hexosaminidase contained in these compositions is stated as having antimicrobial activity.

Decision on novelty

- E1 discloses the antimicrobial activity & the ability to remove already formed biofilm as being advantageous properties of hexosaminidase - component (B) of claim.
- However, E1 teaches that the two do not necessarily go hand in hand but may in fact be alternative properties.
  - “wherein said hexosaminidase enzymes are hexosaminidases having […] antimicrobial activity […], **and/or** the ability to remove biofilm.”

Decision on novelty

- “As regards the detergent composition in question, E1 explicitly and exclusively refers to one of these two alternative properties, namely the antimicrobial activity of the hexosaminidase enzyme. It thus cannot be concluded that these compositions are also used for what is implied by the other property, namely removing an already-formed biofilm.”

Inventive step – problem-solution approach

- Identify the closest prior art (CPA).
- Determine the technical differences of the claim.
- Identify the technical effect(s) provided by the differences.
- Establish the “objective technical problem” to be solved.
- Consider if the claimed invention would have been obvious to the skilled person starting from the CPA.

Inventive step – problem-solution approach

- Identify the closest prior art (CPA).
  - Same technical field.
  - “Most-promising springboard”.
  - Directed to the same purpose / effect / problem to be solved.
  - Number of structural features in common.

Case law – 1st approach to selecting CPA

- Deciding body selects the CPA.
- The skilled person and their expectations, prejudices, knowledge and abilities do not play any role in this selection.
- This approach would imply that each and every disclosure within a document can be selected as the starting point for assessing inventive step.

T1450/16

- The person skilled in the art […] enters the stage only when the objective technical problem has already been formulated. Thus, the skilled person under Article 56 EPC is the person qualified to solve the established objective technical problem […] and not necessarily the person versed in the field of the underlying application or in the field of the selected closest prior art…

Case law – 2nd approach to selecting CPA

- Skilled person comes into play as early as when the CPA is selected.
- Possible to reject an inventive-step attack on the ground that the skilled person would have not realistically selected the specific disclosure on which the attack in hand relies as a starting point.

T710/97

- As a starting point, prior art should primarily be selected which is aimed at the same purpose or effect as the claimed invention […] the intention is to use an initial situation as a basis for the fictitious assessment process, which approximates as realistically as possible the initial situation found by the inventor.

Inventive step over E1 - opponent

- Any detergent composition in E1 can be taken as CPA – including detergent compositions comprising (A) + (B).
- Difference is the suitability to remove an already formed biofilm and the specific use for that purpose.
- E1 generally disclosed hexosaminidase enzymes which had the ability to remove biofilms as a preferred embodiment.
- The skilled person – at most – had to swap the hexosaminidase enzyme contained in the detergent compositions for the one which had the ability to remove biofilms.

Inventive step over E1 - patentee

- E1 only discloses hexosaminidase enzymes in a general form as having antimicrobial activity and the ability to remove biofilms – this disclosure is the CPA.
- Difference is the claimed composition comprises (A).
- Data in the patent showed that combining (A) + (B) improved both suppression of biofilm formation and removal of an already-formed biofilm.
- Surprising technical advantage over the use of hexosaminidase enzymes alone.

Decision on inventive step

- Board agreed that the CPA is a piece of information or technical teaching – each providing a potential starting point.
- Had to select from the two approaches for determining CPA in the case law.

“it is the board's firm conviction that the skilled person is the relevant point of reference right from the start of any inventive-step assessment. Determining whether an invention is inventive involves technical considerations, and those have to be made through the eyes of the skilled person. Excluding the skilled person for part of the inventive-step assessment would lead to artificial and thus technically meaningless results.”

“the consequence of selecting any disclosure within a prior-art document as the starting point, as is possible under the aforementioned first approach, would be that the disclosure coming structurally closest to the claimed subject-matter might always be chosen. However, starting from that disclosure and then possibly denying inventive step on this basis would imply the use of hindsight. More specifically, selecting the disclosure that is structurally closest to the claimed invention would presuppose knowledge of this invention, e.g. in terms of the structure of a claimed compound”

Decision on inventive step

- Only the general disclosure of hexosaminidase enzymes is in relation to the purpose and effect to be achieved by the claimed invention.

Decision on inventive step

- Starting from any of the 7 detergent compositions as per the opponent's approach presupposes knowledge of the present invention, i.e. of the structure of component (A).
- Starting from this disclosure therefore amounts to an ex post facto approach and is based on hindsight.

Discussion points

- Approach to identifying the CPA may be critical to the outcome of inventive step.
- Potentially helpful decision if looking to argue for a restrictive approach for identifying the CPA.
- This goes beyond selecting the CPA document and can also be applied to select the CPA from separate embodiments/disclosures within a document.

T 1989/18 (HOFFMANN-LA ROCHE)

- Legal basis for requiring a description to be amended in line with allowed claims

Background

- EPO Guidelines update in 2021 – e.g. F-IV, 4.3.
- More stringent requirements on description amendments.
  - Deletion of subject matter not covered by claims.
  - Or addition of prominent statements marking as such.
  - Changing “invention” to “disclosure” is not sufficient.
- Based in part on T 1808/06.

Background – T 1808/06

- “In order to meet the requirement of Article 84 EPC that the claims have to be supported by the description, the adaptation of the description to amended claims must be performed carefully in order to avoid inconsistencies between the claims and the description/drawings which could render the scope of the claims unclear.”
- “Any disclosure in the description and/or drawings inconsistent with the amended subject-matter should normally be excised.”

Background – T 1808/06

- “Reference to embodiments no longer covered by amended claims must be deleted, unless these embodiments can reasonably be considered to be useful for highlighting specific aspects of the amended subject-matter.”
- “In such a case, the fact that an embodiment is not covered by the claims must be prominently stated.”

Background

- Somewhat inconsistent implementation.
- Instances of very light touch adaptations by examiners.
- Conversely, instances of strict demands.
- “A complete overhaul is necessary (i.e. cosmetic changes or “light-touch” adaption will not suffice).”

Description

8 A complete overhaul is necessary (i.e. cosmetic changes or "light-touch" adaption will not suffice).

9 Please check that the "field of the invention" section corresponds to the amended claims.

10 **Please replace the "summary of the invention" section with a copy of the amended claims. All subject-matter relating to abandoned matter should be deleted from this section so that there is complete correspondence with the claims on file.**

11 **All clause-like claims (e.g. clauses, items, numbered paragraphs) should be deleted wherever they are located in the application (Guidelines F, IV, 4.4).**

12 **Most importantly of all, the description must nowhere use the terms "invention" or "embodiment" (which implies invention) in connection with subject-matter no longer falling under the claims (examiners are being instructed to take a stricter approach in this respect). The limitations to the claims should be reflected in full in the description. Embodiments in the description which are no longer covered by the independent claims must be deleted (for example if the description comprises an alternative for at least one feature which is no longer covered by the amended claims) unless these embodiments can reasonably be considered to be useful for highlighting specific aspects of the amended claims. In such a case, the fact that an embodiment is not covered by the claims must be prominently stated. The terminology "embodiment of the disclosure" is also forbidden.**

13 **Examples no longer covered by the claims should also be presented as comparative examples.**

14 Other inventions should be removed from the description as far as possible.

15 Remove all subject-matter that is forbidden under Art. 53 (e.g. statements that the invention or embodiments encompass therapy, surgery, treatment etc). **This subject-matter may not be presented as disclosure. If retained, it must be explicitly stated that such subject-matter does not constitute the claimed invention.** Statements that the invention or embodiments encompass agents for use in therapy or surgery are allowed.

Background – T 1989/18

- Appeal of refusal from Examining Division (ED).
- ED found claims allowable
- Held that amendments to the description adapted to those claims did not comply with Article 84 EPC.
- Statements in description considered broader than claims.

Appellant’s arguments

- The amendments to the description were entirely consistent with the claims as found allowable by the ED and did not cast doubt on the granted patent's scope of protection.
- The EPC did not require that parts of the description which were no longer covered by the set of claims intended for grant had to be marked as "non-related disclosure" or even had to be deleted when adapting the description to those claims.

Decision

- Art. 84 EPC (clarity).
- Art. 69 EPC (scope of protection).
- Rule 42(1)(c) EPC (content of the description).
- Rule 48(1)(c) EPC (prohibited matter).

Decision – Article 84 EPC

- Article 84 EPC requires that the claims are clear, i.e. that they properly define and delimit the subject-matter for which protection is sought in understandable and unambiguous terms.
- Only mentions the description in the context of the additional requirement that it must support the claims.
- If the claims are clear in themselves and supported by the description, their clarity is not affected if the description contains subject-matter which is not claimed.
- Art. 84 EPC cannot serve as legal basis for refusal.

Decision – Article 69 EPC

- Article 69 EPC is of no relevance since it is only concerned with the extent of protection conferred as one of the effects of an application or patent.
- Article 69 EPC is not by itself concerned with a requirement of the Convention to be met by an application or patent.

Decision – Rule 42(1)(c) EPC

- The description shall disclose the invention, as claimed, in such terms that the technical problem, […] and its solution can be understood, and state any advantageous effects of the invention with reference to the background art.

Decision – Rule 42(1)(c) EPC

- In the absence of an objection of lack of unity, the board fails to see how the above-mentioned provision could be the legal basis for requiring the applicant, as a general rule, to bring the description in line with claims intended for grant, and to remove passages of the description that disclose embodiments which are not claimed.
- Objected to passages do not impair understanding of technical problem and its solution.
- Rule 42(1)(c) EPC cannot serve as legal basis for refusal.

Decision – Rule 48(1)(c) EPC

(1) The European patent application shall not contain:

(a) statements or other matter contrary to "ordre public" or morality;

(b) statements disparaging the products or processes of any third party or the merits or validity of the applications or patents of any such party. Mere comparisons with the prior art shall not be considered disparaging per se;

(c) any statement or other matter obviously irrelevant or unnecessary under the circumstances.

Decision – Rule 48(1)(c) EPC

- Preparatory documents provide no guidance as to what could amount to "obviously irrelevant or unnecessary" statements or matter.
- Points (a) to (c) of Rule 48(1) EPC are in the order of their offensiveness, ranking from high to low.
- Difficult to conceive that the legislator intended […] to provide a ground for refusal based on the inclusion of merely "irrelevant or unnecessary" matter.

“In view of the above considerations, the board fails to see how the aforementioned provisions of the EPC, or any others, can lead to the requirement that embodiments disclosed in the description of an application which are of a more general nature than the subject-matter of a given independent claim must constitute potential subject-matter of a claim dependent on that independent claim.”

Discussion points

- Currently an isolated case.
- No reference to T 1808/06 or possible discrepancies between decisions.
- Useful if wish to push back against strict requirements to amend descriptions?
- EPO Guidelines to be updated in March 2022 (preview in February 2022) – workshop to discuss adaptation of the description took place in November 2021.

UP & UPC

The Provisional Application Period of the Unified Patent Court (UPC) has now begun, allowing preparations for the unitary patent and UPC to start.

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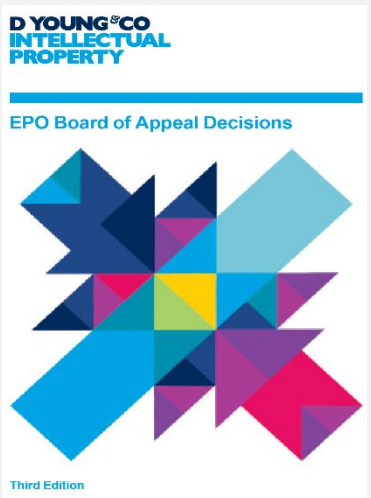

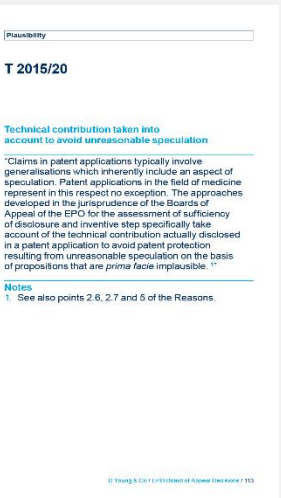

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Any questions…?

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