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European Biotech Case Law Webinar

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Speakers, slides & questions

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Webinar agenda

- Clinical trials protocols as prior art
  - **T 1123/16** *(Eosinophilic bronchitis/GLAXO)*
  - **T 2963/19** *(Liposomal irinotecan/IPSEN)*
  - **T 108/21** *(Treatment of multiple sclerosis/NOVARTIS)*
- Sufficiency of antibody claims
  - **T 2416/18** *(Cross-neutralising antibodies/POMONA RICERCA)*
  - **T 317/20** *(NGF antagonist for treatment of osteoarthritis/RINAT)*
  - **T 499/18** *(Compositions and methods for treating cancer/ONCOMED)*

- T 1123/16 *(Eosinophilic bronchitis/GLAXO)*
  - Clinical trial protocol as closest prior art

T 1123/16 – Claims

1. *A composition comprising at least one neutralising humanised anti-human-IL-5 antibody for use in treating a human suffering from steroid-dependent eosinophilic bronchitis,* ***characterised in that*** *the steroid is prednisone and wherein the prednisone is reduced by at least about 90% in said human after treatment.*

= an antibody composition for treating steroid-dependent eosinophilic bronchitis (EB), and resulting in 90% reduction of steroid

T 1123/16 – Background

- Opposition rejected by OD
- OD held that the patent as granted complied with the requirements of sufficiency of disclosure, did not add matter, was entitled to its priority, and was novel and inventive.
- Appellant contested the decision in relation to the findings on priority, novelty and **inventive step.**

T 1123/16 – Closest Prior Art

- D1 describes a phase II clinical trial.
- The purpose of the clinical trial is "to determine if the treatment with anti-IL-5 antibody has a prednisone-sparing effect in patients with symptomatic eosinophilic bronchitis (with or without asthma)“.
- The BOA considered the disclosure of this phase II clinical trial to constitute an appropriate starting point for assessing inventive step.
- It concerns the treatment of patients with the same medical condition (i.e. steroid-dependent EB) using the same substance (i.e. a humanised antibody to IL-5) with the same objective (i.e. a reduction in prednisone administration).

T 1123/16 – Objective Technical Problem

- The claims differed from the disclosure of D1 in that:
  i. an effective treatment is not inferable from D1 since it does not disclose any results of the clinical trial
  ii. the claim specifies a minimum level of prednisone-sparing effect (90%), which is not specified in D1.
- The patent disclosed the results of the clinical trial as known from document D1, including a prednisone sparing effect as required by the claim.
- The technical effect of the above differences is that an effective treatment of prednisone-dependent EB is provided allowing a 90% reduction of prednisone.
- The objective technical problem may thus be formulated as the provision of an effective treatment of prednisone-dependent EB with reduced side effects.

T 1123/16 – Obviousness

- Does the prior art provide the skilled person with a **reasonable expectation** that an anti-IL-5 antibody would be effective in the treatment of prednisone-dependent EB with less side effects?

T 1123/16 – Case law

- **T 2506/12** (para 3.10)

"…the information was available that the envisaged combination treatment **was considered by pharmaceutical researchers with an expectation of success sufficient to justify a clinical phase I trial**. In this context it is pointed out that drug compounds to be used in a clinical trial with human subjects are not selected based on a general "try-and-see" attitude, but based on existing favourable scientific data, for both ethical and economical reasons. **Thus a clinical trial is not a mere screening exercise**."

T 1123/16 – Case law

- **T 239/16** (para 6.5)

"…the mere fact that an active agent selected from the group of bisphosphonates is being tested in a clinical study for the treatment of osteoporosis … **leads to an expectation of success,** due to the fact that clinical studies are **based on data obtained by pre-clinical testing** both *in vitro* and in animals and require authority approval which takes ethical considerations into account. This means in the present case that the skilled person would expect all study arms to treat osteoporosis effectively, **unless he was dissuaded from this by the prior art."**

- In other words, unless the state of the art provided the skilled person with an **expectation of failure.**
- The board notes that, in decision T 239/16, no relevance is given to the phase of the clinical trial.

T 1123/16 – Obviousness

- It therefore remains to be assessed whether the state of the art provided the skilled person with the **expectation that the treatment would fail.**
- The respondent submitted various documents concerning **asthma treatment**, such as documents D6, D8, D13, D15, D16 and D27, in fact showed that there was a **negative expectation** regarding a successful treatment based on an antibody to IL-5.
- The board considered that this line of argument did not seem to be pertinent to the claim at hand because it does not require that the patients suffer from asthma
  - Effects in asthma patients are not necessarily indicative of effects in EB patients since the role of eosinophils in asthma is not fully elucidated

T 1123/16 – Obviousness

- The skilled person had **no reason** to expect that the treatment described in D1 **would not succeed**.
- The solution provided in the claim, specifying the level of reduction in prednisone to be 90%, **is a consequence** of pursuing the treatment described in D1, for which the skilled person had a **reasonable expectation** that a prednisone reduction would be achieved without exacerbations.
- The specific level of reduction of 90% recited in the claim does not play a role in the assessment of what the skilled person would do when faced with the objective technical problem.
- Claim 1 therefore lacks an inventive step.

T 1123/16 – Non-admittance of AR3

- Auxiliary request 3 was withdrawn during the oral proceedings. The withdrawal was unequivocal.
- The proprietor subsequently informed the board that they intended to resubmit auxiliary request 3.
- The board decided not to admit auxiliary request 3 into the proceedings:
  - The board had to consider the request as if it were filed for the first time during the oral proceedings and at a very late stage.
  - It could have been filed earlier (it was!).
  - Nothing happened during the oral proceedings (in particular after the request was withdrawn) which could have justified the filing of a new request.

T 1123/16 – Take home

- Clinical trial protocols provide a reasonable expectation of success (in the absence of art providing an expectation of failure).
- Reciting an unknown but inherent result of the obvious treatment has no bearing on the assessment of inventive step.
- Take care when withdrawing auxiliary requests!

- T 2963/19 *(Liposomal irinotecan/IPSEN)*
  - Clinical trial protocol without results – expectation of success?

T 2963/19 – Claims

1. Liposomal irinotecan for use in a method of treating pancreatic cancer in a human patient…..wherein the patient has failed prior treatment with gemcitabine or become resistant to gemcitabine, the method comprising co-administration of an effective amount each of **liposomal irinotecan, 5-fluorouracil (5-FU) and leucovorin** to the patient in at least one cycle wherein the cycle is a period of 2 weeks and, for each cycle:

   a) liposomal irinotecan is administered to patients not homozygous for the UGT1A 1 *28 allele on day 1 of each cycle at a dose of 80 mg/m^2 and to **patients homozygous for the UGT1A1 *28 allele on day 1 of cycle 1 at a dose of 60 mg/m^2** and on day 1 of each subsequent cycle at a dose of 60 mg/m^2 or 80 mg/m^2;

   b) 5-FU is administered at a dose of 2400 mg/m^2; and

   c) leucovorin is administered at a dose of **200 mg/m^2 (l form) or 400 mg/m^2 (l+d racemic form)**;

and wherein in each cycle, the **liposomal irinotecan is administered prior to the leucovorin, and the leucovorin is administered prior to the 5-FU**.

= a combination therapy for treating pancreatic cancer.

T 2963/19 – Background

- Patent opposed on grounds of lack of inventive step and insufficiency.
- Patent revoked by OD for lack of inventive step, starting from document D15b as closest prior art.
- The proprietor appealed.

T 2963/19 – D15b

- D15b describes a randomized, open label Phase 3 study of
  - Arm A: “MM-398” (monotherapy)

  or

  - **Arm C: “MM-398” in combination with 5-FU and Leucovorin (triple therapy)**

  versus

  - Arm B: 5-FU and Leucovorin

  in treatment of patients with metastatic pancreatic cancer who have failed prior gemcitabine-based therapy.
- D15b did not explain the meaning of "MM-398” – however this was known from other documents to be liposomal irinotecan
- BOA considered arm C to be suitable starting point

T 2963/19 – Inventive step

- Differences between the claimed subject-matter and arm C of the protocol in D15b:
  - the actual **effective and safe treatment** of the patients
  - specification of the order in which the drugs are administered
  - the distinction in the starting dose of liposomal irinotecan depending on the status of the UGT1A1*28 allele and

T 2963/19 – Known challenges

- D23 - the development of therapy of gemcitabine refractory pancreatic cancer represents a **particular challenge** taking account of the poor prognosis and **low success rates of clinical trials**
- D37 and D38 - confirm in this context that the approval of a clinical study depends on the assessment of the foreseeable risks in relation to the anticipated benefit in terms of relevance of the findings, which **does not necessarily imply an expected positive outcome** and does not represent a scientific advice on the development programme of the investigational product tested

T 2963/19 – So no reasonable expectation from D15b

- The Board is therefore **not convinced** that the mere fact that document D15b reports the testing of the dosage regimen in a Phase 3 clinical trial already by itself **provided the skilled person with a reasonable expectation** that the treatment under investigation would be safe and effective.
- The considerations in **T 239/16** regarding the expected success following the approval of a clinical trial are evidently **closely linked to the further circumstances of the case** decided therein and **cannot be extrapolated** to the present appeal case.

T 2963/19 – D15b in context

- However, the presentation of the triple dosage regimen in D15b is **not to be considered by itself**
- D15b was preceded by reports of beneficial effects in Phase 1 investigations
- And also reports of beneficial effects of non-liposomal irinotecan with 5-FU and leucovorin in Phase 2 studies.
  - The patentees themselves had relied upon these disclosures in their arguments for sufficiency and plausibility!

T 2963/19 – Decision of the board

- BOA considers that in as far as the patent proposes the claimed dosage regimen to be **safe and effective** in view of considerations based on information which was essentially already available, the **same considerations apply** in the assessment whether following the presentation of the clinical trial in D15b a positive outcome for the described triple therapy could **reasonably be expected**.
- Accordingly, claim 1 obvious in view of D15b.

- T 0108/21 *(Treatment of multiple sclerosis/NOVARTIS)*
  - Clinical trial protocol without results – prior art teaches away from an expectation of success?

T 0108/21 – Claims

1. *A S1P receptor modulator for use in the treatment of relapsing-remitting multiple sclerosis, at a **daily dosage of 0.5 mg p.o.**, wherein said S1P receptor modulator is **fingolimod** in free form or in a pharmaceutically acceptable salt form*

T 0108/21 – Background

- Application rejected by Examining Division for lack of **novelty**
- Appellant appealed the decision to refuse grant
- Appellant contested the decision in relation to the findings on **novelty**, and submitted arguments relating to **inventive step** and sufficiency of disclosure
- The Board of Appeal disagreed with the Examining Division with regard to the **novelty** objection and so proceeded to assess inventive step objections.

T 0108/21 – Closest prior art

- D10 discloses a successful Phase II clinical trial establishing the therapeutic efficacy and tolerability of a daily fingolimod **dose of 1.25 mg** in patients with RRMS.

- D10 also announced a Phase III clinical trial with a patient group set to receive a daily fingolimod **dose of 0.5 mg** in patients with RRMS.

T 0108/21 – Inventive step

- The subject-matter of claim 1 differs from the prior art document D10 in that fingolimod is administered at a **daily dose of 0.5 mg**.
- The Board of Appeal was satisfied the claimed dosage regimen provides an effective therapeutic treatment of RRMS.
- Objective technical problem is the provision of further means to effectively treat RRMS.

T 0108/21 – Obviousness

- Does the prior art provide the skilled person with a **reasonable expectation** that a dosage of 0.5 mg of fingolimod would be effective in treatment of RRMS?
- Board judged that the announcement of a Phase III clinical trial with a dose of 0.5 mg **would** have provided the skilled person with a reasonable expectation of success, **unless a teaching in the prior art** would have dissuaded the skilled person from considering the dosage.

T 0108/21 – Teaching away

- The Board concluded that the teachings of documents D26 and D27 in combination with the teaching of D23 would lead the skilled person to conclude that an oral daily dose of 0.5 mg fingolimod would be insufficient and not therapeutically effective.
- D10 would “have given the skilled person hope of success but not a reasonable expectation of it”
- As a result, the Board decided that claim 1 involved an inventive step over the prior art D10

T 2963/19 and T 0108/21 – Take home messages

- A clinical trial protocol alone may not provide a reasonable expectation of success…
- In particular, if there are existing prejudices relating to the protocol (e.g. a “particularly difficult challenge”) or other prior art that teaches away from a reasonable expectation of success
- Will likely be highly dependent on the facts of each case.

- T 2416/18 *(Cross-neutralising antibodies/POMONA RICERCA)*
  - Functional antibody claim supported by a single example

T 2416/18 – cross-neutralising antibodies

- Claim 1:

  1. *A human monoclonal antibody directed against influenza A virus hemagglutinin antigen, characterized in that it is **capable of binding to and neutralizing a plurality of subtypes of the influenza A virus**, wherein said plurality of subtypes comprises at least one influenza A virus subtype containing hemagglutinin **H1** and at least one influenza A virus subtype containing hemagglutinin **H3**.*

- = an antibody cross-neutralising both H1 and H3 subtypes.
- Revoked at Opposition - insufficiency.

Art. 83 EPC: fundamental case law

- Article 83 EPC requires that the application disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art. In the case at hand, to carry out the claimed invention, the skilled person must be able, on the basis of the disclosure in the application and of common general knowledge, to obtain the claimed human mAbs without undue burden.
  - *Case Law of the Boards of Appeal, 9th edition 2019, section II.C.4.1.*

- "substantially all" of the claimed Abs
  - *Case Law of the Boards of Appeal, 9th edition 2019, section II.C.5.4.*

T 2416/18: background

- Disclosure of the patent:
  - same-subtype (“heterologous” or “homosubtype”) immunity is common in humans
  - immunity to a *different* subtype (**“heterosubtype”** immunity) is *“**extremely rare** both in case of natural infection and in case of vaccination”* and *“achieving mAbs with such properties has proved to be “**extremely difficult**”.*
- Patent provided: Fab28, a single cross-neutralising antibody
- Patent further disclosed: **selection criteria** for patients
  - do the selection criteria allow reliable identification of individuals producing further cross-neutralising antibodies?

T 2416/18: patient selection criteria

(1)- *between 25 and 55 years of age;*

(2)- *recent pathological medical history, for the ten years preceding the study, negative for clinical influenza syndromes;*

(3)- antibody titer higher than 1:1000 against virus isolates, subtypes H1N1 and H3N2 responsible for the annual epidemics during the five years preceding the study;

(4)- high neutralizing titer (IC50 >= 1:400) against virus isolates, subtypes H1N1 and H3N2 responsible for the annual epidemics during the five years preceding the study;

(5)- detectable neutralizing titer (IC50 >=l:20) against two reference subtype A virus isolates (A/PR/8/34 subtype HlNl; A/PC/1/73 subtype H3N2);

(6)- *no prior anti-influenza vaccination;*

(7)- compliance to receive anti-influenza vaccination

T 2416/18: decision of the BoA

- Selection criteria find people likely to be immune to both H1 and H3 subtypes, but the ability to produce a *cross-neutralising antibody* is a mere hypothesis.
- More likely is that the patient simply has two different antibodies, one for each of H1 and H3.
- No evidence that the single isolated example (Fab28) would have been identified by the selection criteria *versus* a “brute force” large scale screen.
- Fab28 - a “single lucky event”
- Art. 83 EPC contravened. Appeal dismissed; patent finally revoked.

T 2416/18: lessons

- Sometimes there is no need for experimental evidence to challenge a patent under Art. 83 EPC, even when there is a working example.
- Attacking the rationale for extrapolating from this example (here, selection criteria) can be an effective strategy.
- This can be done by logically challenging the disclosure of the patent itself.

- T 317/20 *(NGF antagonist for treatment of osteoarthritis/RINAT)*
  - Plausibility of medical use claim

T 317/20 – NGF antagonist for treatment of osteoarthritis

- Claim 1:

  1. *Use of an effective amount of an anti-NGF antagonist antibody in the manufacture of a medicament for **improving physical function** in an individual having osteoarthritis.*

- = an anti-NGF antagonist antibody for use in improving physical function in OA patients.

- First instance: sufficiently disclosed.

  - O failed to provide evidence that the antibody would ***not*** improve physical function, in the subgroup of **an OA patient who was not experiencing pain**.

Case law: “suitable for” test for medical claims

- The application must disclose that the claimed product is suitable for the claimed therapeutic application, here for improving physical function in an individual having osteoarthritis (unless this is already known to the skilled person at the priority date).
  - *Case Law of the Boards of Appeal, 9th edition, 2019, II.C.7.2., see specifically T 609/02*

T 317/20: opponent's appeal case

- "suitable for" test not met, i.e. anti-NGF antagonist antibody is not suitable for the improvement of physical function in OA patients.
  - not shown for the OA patient subgroup who **did not experience pain**, but did have impaired physical function.
- All patients in the Example suffered from pain. Thus, no experimental proof that physical function can be improved for any patient, inc. the subgroup where there is no pain.
- Example used a questionnaire wherein scores for pain reduction and physical function could be interrelated, i.e. analgesia makes it easier to move.
- Hence, the invention is not reproducible across the whole claim scope.

T 317/20: decision of the BoA

- Patentee: No evidence to show that it *wouldn't* work.
- BoA: In the absence of experimental proof of treatment of these patients, comprehensible and plausible arguments can substantiate serious doubts as to whether the skilled person could carry out the invention as claimed, and evidence in the form of experimental data is not necessarily required (T 347/15, Reasons 2.2.2).
- Patentee: an occasional failure in the treatment of a small patient subgroup did not result in an insufficiency of disclosure.
- BoA: the invention has to be reproducible in the whole range that is claimed, and improvement of function in OA patients is a limiting purpose-feature.

T 317/20: decision of the BoA

- R. 24:

  “the failure of treating an entire patient subgroup, albeit small, which is distinguished from the patient group as a whole by its pathological status, is not equivalent to an occasional failure in treating some patients within the patient group. ***The size of the patient subgroup is not decisive*** *for the assessment of sufficiency of disclosure of the invention as defined in the claim.”*

  - The patent was revoked

T 317/20: lessons

- Another case with no need for experimental rebuttal.
- When dealing with a claimed therapeutic indication, once it is determined that suitability is not shown (even only for a particular patient subgroup), there is no need to show that it *wouldn't* work.
- Opponent only had to determine that the treatment had not been shown to be suitable for the subgroup.
- Opponent did this by closely examining the details of data (questionnaire results).

- T 499/18 *(Compositions and methods for treating cancer/ONCOMED)*
  - Plausibility of attaining a functional feature

T 499/18 – compositions and methods for treating cancer

- Claim 1:

  1. *An isolated monoclonal antibody that specifically binds to a human R-spondin (RSPO) protein and inhibits growth of a solid tumor comprising solid tumor stem cells, wherein* ***the antibody disrupts binding of the RSPO protein to a leucine-rich repeat-containing G protein-coupled receptor (LGR) protein, wherein the LGR protein is LGR5****; and/or disrupts RSPO activation of LGR5 signaling.*

- = an antibody which disrupts the binding between the ligand RSPO and its receptor LGR5, to inhibit tumour growth.

- Revoked at first instance - insufficiency

T 499/18: decision at first instance

- Patent disclosed: LGR5 is expressed in many tumours.
- Patent showed: experiments on HEK293 cells:
  - RSPO increases oncogenic (Wnt/beta-catenin) signalling;
  - Signalling is reduced by adding more soluble LGR5.
  - Conclusion: RSPO and LGR5 interact in HEK293 cells to modulate signalling.
- OD: On the balance of evidence, HEK293 cells did not actually express LGR5. The experiments could not demonstrate any actual interaction between RSPO and LGR5.
  - Hence not plausible that the claimed antibodies blocking this interaction would inhibit beta-catenin signalling and tumour growth.

T 499/18: relevant evidence

- D14/D15: specific evidence showing HEK293 cells which do not express LGR5 protein. There was a comparison to the closely related LGR4, which was shown to be expressed instead.
- D25: a general teaching showing HEK293 cells which express LGR5 **mRNA** – from which the skilled person would expect LGR5 protein to be expressed.
- OD: much more weight given to D14/15 because this evidence specifically investigates protein levels as opposed to mRNA levels, and considers the very similar receptor LGR4, which was not investigated in D25.

T 499/18: decision of the BoA

- The fact that mRNA was measured in D25 is not relevant.
- The fact that D14/D15 is more specific and gives evidence relating to another closely related protein is no reason to give it a “much higher weight”.
- D14/D15 is an isolated finding.
- Not established on the balance of probabilities (one document on each side) – that **all** HEK293 cells do not express functional LGR5 protein.
- No serious doubts to challenge the hypothesis based on the Example underpinning the claimed invention.

T 499/18: outcome & lessons

- Appeal allowed; case remitted to OD.
- Another case investigating the level of evidence required to substantiate an attack under Art. 83 EPC
- Sufficiency was ***initially*** challenged successfully without experimental evidence. This was done by O asserting, on the balance of probabilities, that a fact underpinning the invention was incorrect.
- Patentee used same evidence to tip the balance of probability in their favour.
- In this case, the burden of “serious doubts” reverted back to the opponent, who could not discharge it.

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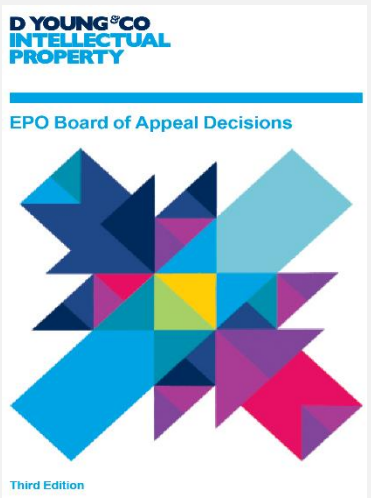

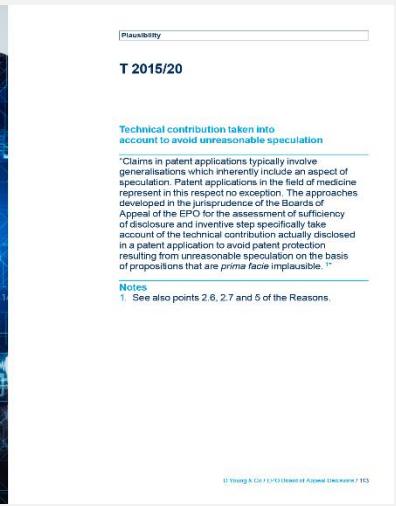

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