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European Biotech Case Law Webinar

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Slides and a recording of this webinar will be emailed to you later this week. Email us direct after the webinar with any follow up questions.

Webinar agenda

- T 2344/19
  - Definition of patient sub-groups
- T 0670/20
  - Public disclosures associated with clinical trials
- T 0605/20
  - Formulation of the technical problem
- Update on Rules of Procedure of the Boards of Appeal – 2020
  - Admissibility during appeal proceedings

T 2344/19

H. Lundbeck A/S

- Patient sub-groups

Patient sub-groups

Patient sub-groups case law – **T 19/86**, **T233/96**, **T 1399/04** and others

T 1491/14:

"In the course of the oral proceedings before the board, the patent proprietors put forward that the criteria for a patient group rendering a previously known therapeutic method novel are that:

i) The patient group is not disclosed in the relevant prior art.

ii) The patients belonging to the group can be distinguished from those of the prior art by their ***physiological or pathological*** *status.*

iii) There is a functional relationship between their characterising physiological or pathological status and the therapeutic treatment and thus the selection of the patients is not arbitrary.

The opponent did not contest this, and the board agrees that – although the case law of the board of appeal does not seem to provide fixed criteria for a patient group – a patient group fulfilling those three criteria is anyhow suitable to render the claimed subject-matter novel."

Patient sub-groups T 1399/04 (Schering Corporation)

The use of ribavirin in association with an effective amount of interferon alpha for treating hepatitis C infection :

- administration for a time period of 40-50 weeks
- the patient is an antiviral treatment naive patient
- the patient is one having a HCV genotype type 1 infection
- the patient has a viral load of greater than 2 million copies per ml of serum

Patient sub-groups T 0694/16 (N.V. Nutricia)

Composition comprising (a) one or more of DHA, DPA and EPA, (b) uridine, deoxyuridine, uridine phosphates, uracil or acylated uridine derivatives, and (c) a methyl donor, wherein the composition further includes vitamin B12 and folate

for use in the prevention or delay of the onset of dementia in a person having CSF markers characteristics of a prodromal dementia patient.

Patient sub-groups T 0694/16

- the issue of whether patients displaying the markers of claim 1 were present among a population of previously treated patients and were already "inevitably" or "inherently" treated is irrelevant for assessing novelty in the present case.
- The only thing which counts is that the prior art does not disclose a method whereby a patient or a group of patients displaying the relevant CSF markers but not affected by dementia was purposively and selectively targeted for carrying out the preventive treatment defined in claim 1.

Patient sub-groups T 0694/16

- The claimed method can be seen as one which aims at hitting a target which is hidden behind a screen, but the screen reveals a spot which allows the position of the target to be actively aimed at. This allows hitting the target precisely while reducing the risk of hitting other objects present behind that screen.

T 2344/19 - claim

Claim 1

[Vortioxetine] and pharmaceutically acceptable salts thereof for use in the long-term treatment of depression or anxiety **in a patient who has previously received medication for the treatment of said disease which medication was ceased due to weight gain related adverse events**, wherein long-term treatment refers to a treatment period above 12 weeks.

T 2344/19 - novelty: opponent's arguments

- Patients' decisions to cease a previous medication did not make them physiologically and pathologically different from patients deciding not to cease previous medication.
- A patient's decision to cease or not to cease a line of treatment was the mere result of a mental act which was not suitable to distinguish the claimed subject-matter from the prior art.
- A patient group defined by merely "subjective" decisions by the patients could not be a limiting technical feature.

T 2344/19 – novelty

"The patient's decision to cease medication for the treatment of depression or anxiety as such is not defined in the claims under consideration… Consequently, no mental act or thought process forms part of the claimed subject-matter…

The development of certain side-effects reflects a certain physiological and/or pathological status of the patients concerned. ***The development of these side-effects during treatment for depression or anxiety creates a link between the patients, their physiological and/or pathological status, and the therapeutic treatment.*** *The patient group under consideration is thus a technical feature of the claims.*

The technical feature defining the patient group under consideration is not disclosed in any of the documents cited..."

T 2344/19 – inventive step (CPA)

- Parties agreed D7 was CPA – described weight gain as an adverse effect of psychotropic drugs, medication should be switched to another drug.
- Data in the patent:
  - Patients on vortioxetine do not gain weight long-term above what can be expected in the population under consideration.
  - No comparison to another potential switch drug – this fact has to be reflected in the formulation of the technical problem.
  - Technical problem – provision of a further active for long-term treatment of depression or anxiety in a patient group prone to weight gain related adverse events.

T 2344/19 – inventive step

Closest prior art discloses that short-term clinical trials, which last 6 to 8 weeks, may underestimate the long-term effects of weight gain.

Established in art (e.g. D6) that vortioxetine has no short-term (up to 6 weeks) weight gain effects.

- **But nothing known about long-term (12 weeks or more) effects on weight gain.**
- no conclusion on the occurrence of weight related side-effects in the treatment with vortioxetine may be drawn that goes beyond mere speculation.

T 2344/19 – expectation of success versus hope to succeed

- The case at hand relates to the treatment of depression or anxiety. As clearly established in the art, weight gain related adverse effects put the patients at considerable risk - coronary heart disease, hypertension etc - but, and this is also of the utmost importance, they may also lead to non-compliance, with the probability of relapse and subsequent (re)hospitalisation.
- It is clear that the person skilled in the art would have avoided the administration of any psychotropic drug for which long-term weight gain related side-effects had not been excluded.

T 2344/19 – expectation of success versus hope to succeed

"*…the person skilled in the art would have needed…* ***a strong expectation of success.*** *Any treatment undertaken with a mere hope to succeed, in the present case a treatment where short-term side-effects had been excluded but nothing was known on long-term side-effects, would not have been envisaged by the person skilled in the art.*

Consequently, since no information on long-term weight gain related side-effects was known for vortioxetine, the person skilled in the art would not have considered vortioxetine for solving the technical problem stated above, and thus ***would not have arrived at the claimed subject-matter.***"

T 2344/19 – inventive Step – D3

- Inventive step also assessed from D3 as CPA – disclosed treatment of depression or anxiety with vortioxetine **i.e. starting from the drug.**

"*the person skilled in the art had not been aware that vortioxetine had a favourable side-effect profile concerning weight gain in long-term treatments.*

Consequently, the person skilled in the art would have had ***no incentive to administer vortioxetine*** *as second-line treatment to a group of patients known to have had issues with weight gain related adverse events in a previous treatment of depression or anxiety.*"

“Try and See” approach - Case Law of the Boards of Appeal

- When neither the implementation nor the testing of an approach suggested by the prior art involves any particular technical difficulties, the consideration that the skilled person would have at least adopted a "try and see" attitude is a reason for denying inventive step (see e.g. T 333/97, T 377/95 of 24 April 2001, T 1045/98, T 1396/06, T 2168/11).
- In such situations the concept of "reasonable expectation of success" does not apply (T 91/98, T 293/07 and T 259/15). The skilled person would prefer to verify whether the potential solution he had conceived worked, rather than abandon the project because success was not certain ("try and see" approach).

T 2344/19 – summary

- Experience of a particular side-effect in previous treatment defines a patient sub-group.
- “Strong” expectation of success required for the second-line treatment be obvious – lack of data in the prior art on the specific side-effect enough in this case.

T 0670/20
SANKYO

- Clinical trials and public disclosure

T 0670/20: overview

- The patent related to a pharmaceutical composition comprising a coated tablet having edoxaban as active ingredient.
- The tablet allegedly exhibited excellent dissolution properties.
- The board of appeal considered whether patients in a clinical trial of administration of edoxaban in the claimed tablet form prior to the priority date were under obligation of confidentiality, or if the composition had been made publically available.

T 0670/20: background

- Two clinical trials (NCT00107900 and NCT00398216) described in D19 and D20.
- The appellants did not contest that the investigators involved in the trials were bound to confidentiality and could therefore not be considered as part of the public.
- But were the patients members of public?
- Tablets were provided to patients discharged from the hospital prior to the end of the treatment regime, for use at home.
- The assessment of novelty depends on whether participating patients who received the tablets are to be considered as members of the public who were free to dispose over the provided tablets and thus theoretically in a position to investigate the internal structure of the tablets.

T 0670/20: opponents' arguments

- Opponents argued patients were not bound by any confidentiality agreement.
  - Cited documents D19 and D20 actually encouraged participants to discuss their participation in the clinical trials with their doctor, family members, and friends.
- The opponents further argued it would be unethical to bind patients to a confidentiality agreement that would prevent them from discussing the trial with their doctor, family members and friends.
- Whilst the participants in the trial had been requested to return their unused tablets, in the absence of any legal sanction no parallel to a confidentiality agreement could be assumed on such basis, particularly as full compliance would be unlikely.
- Parallels drawn to T 7/07 which also dealt with clinical trials that had occurred before the priority date was appropriate in this case.

T 0670/20: considerations of the Board (1)

- According to the clinical trial documents, the investigators in the trials were instructed to ensure drug accountability and to monitor treatment compliance by taking account of the unused medication returned by the patients discharged from hospital.
- The board summarised:

"The clinical trials were carried out in accordance with the EMEA Guidelines for Good Clinical Practice. These…explicitly require adherence to the prescribed protocol and assurance of drug accountability. This set-up…implies that the patients who decided to participate in the trials agreed…to use the provided medication according to instruction or to return the unused medication. Accordingly, the participating patients…entered into a special relationship with the investigators…and were with regard to the provided tablets not members of the public that could freely dispose over these tablets."

T 0670/20: considerations of the Board (2)

- D19 and D20 encouraged participants to discuss their participation in the clinical trial with their doctors, family members and friends. However the board saw no reason that the absence of a duty of confidence with regards to **participation** in the trial should affect the obligations of the participant with regarding the **use and return of the tablets** provided to them.
- The board summarised:

  *"The patients' agreement to use the provided medication according to instruction or to return the unused medication obliges the patient… therefore disqualifies the patients as members of the public with respect to the medication provided to them. The possibility of non-compliance to the instructed use and return of the tablets by participating patients **does not affect the essence of this agreement**".*

T 0670/20: considerations of the Board (3)

- The board dismissed the relevance of arguments based upon T 7/07.
  - In T 7/07, on the basis of available information, the sponsor of the trial had effectively lost control over the drugs after they had been handed out to participants of the trial.
  - In T 7/07, not all of the unused study drugs were returned. Therefore, it appears that after having handed out the drugs the respondent effectively lost control over them as the participants in the clinical trials were in no way barred from disposing of the drugs as they wanted.
  - The Enlarged Board emphasises that there is no support in the EPC that the public should have particular reasons for analysing a product put on the market in order to identify its composition or internal structure.
- Thus in view of all evidence submitted in the present case the board concluded in line with the opposition division that the clinical tests were not public, in contrast to the decision T 7/07.

Comparison to case law (T 7/07)

Why did the decision differ?

- In T 7/07, the Board concluded tablets were publically available:
  - Large number of patients given tablets to take home with them and for use over a long period of time.
  - Not all of unused drugs returned – **"lost control"** over the drugs.
- In T 0670/20, the Board concluded that patients **did** have an obligation to use medication in accordance with instructions and could not be considered free members of the public:
  - "Special relationship" due to set up of the trial.
    - Patients agreed to use the medication as instructed or **return unused medication**.
  - Possibility of non-compliance does not affect the essence of this agreement.

T 0670/20 – inventive Step

Bonus effect?

The opponents argued that the claimed tablets should be denied an inventive because the defined coated structure and the defined excipients were entirely conventional for immediate release tablet formulations - any unexpected dissolution characteristics would represent a mere bonus effect.

Case law on bonus effect requires that the skilled person was actually bound to arrive at the claimed subject-matter, for instance because alternatives were absent for solving a realistic technical problem and the skilled person was thus in a so-called "one-way street" situation.

Argument failed here as there were alternatives.

Claims therefore inventive.

T 0670/20: take-home messages

- Information disclosure is a constant challenge of running clinical trials.
- Companies should always be aware of the potential for public disclosures, which can seriously affect patentability.
- T 0670/20 gives reassurance that **appropriately** constructed trials can infer some duty of confidentiality with regard to medicament composition– even if taken home.

T 0605/20

Novo Nordisk A/S

- Formulation of the technical problem

Background

- EP1687019 relates to a pharmaceutical formulation comprising liraglutide and propylene glycol
- GLP-1 receptor agonist - type 2 diabetes, obesity and chronic weight management
- Production of peptide formulations and administration by injection
- Appeal: patent maintained as granted during opposition

Claim 1 on appeal

1. A pharmaceutical formulation comprising the peptide Arg^{34}, $Lys^{26}(N^{\varepsilon}\text{-}(\gamma\text{-}Glu(N^{\alpha}\text{-}hexadecanoyl)))\text{-}GLP\text{-}1(7\text{-}37)$ and propylene glycol, wherein said propylene glycol is present in said formulation in a final concentration of from 1 mg/ml to 100 mg/ml, and wherein said formulation has a pH of from 7.0 to 10.0.

Arg^{34}, $Lys^{26}(N^{\varepsilon}\text{-}(\gamma\text{-}Glu(N^{\alpha}\text{-}hexadecanoyl)))\text{-}GLP\text{-}1(7\text{-}37)$ – “Liraglutide”

Prior Art – D3

- Pharmaceutical composition
  - Comprising modified GLP-1 compound – specifically liragultide
  - pH 7-10
  - May comprise an isotonic agent
  - May be propylene glycol, **but** preferably mannitol or glycerol
  - Isotonic agent may be from 1-50 mg/ml

Decision on novelty

- D3 does not directly and unambiguously disclose a composition according to claim 1 **comprising propylene glycol in a concentration of 1-100 mg/ml**.

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
- Formulate the “objective technical problem” to be solved
- Consider if the claimed invention would have been obvious to the skilled person starting from the CPA

Technical difference and effect over D3

- Propylene glycol vs mannitol or glycercol
- Avoided formation of deposits on equipment and clogging of injection devices
- Reduced gel-like drops on injection needle

‘Problem inventions’

- Discovery of an **unrecognised problem** may in certain circumstances give rise to patentable subject-matter in spite of the fact that the claimed solution is retrospectively trivial and in itself obvious.
- To address a problem simply by looking for ways of overcoming difficulties arising in the course of routine work did not constitute inventiveness.
- The appreciation of a technical problem could thus only contribute to the inventive step **in very exceptional circumstances**.

Inventive step analysis - opponent

- Use of mannitol as described in D3 **inevitably confronts** the skilled person with the problem of formation of deposits on equipment and clogging of injection devices
- Problem of the formation of deposits and clogging of devices concerned a **convention technical problem**.
- Would be addressed in the course of the skilled person's **normal activities**.

Inventive step analysis - opponent

- Skilled person was aware of tendency of mannitol to crystallise
- Routine practice identify mannitol as the cause of the problematic deposits
- Propylene glycol was an obvious replacement
  - Known to be fluid state at relevant temperatures + suitability as an isotonic agent was known (including from D3)

Inventive step analysis - patentee

- Formation of deposits / clogging of needles / occurrence of gel-like drops **would not necessarily manifest themselves upon the practical implementation of D3.**
- These problems were only identified in the patent.
- Avoiding the formation of deposits and clogging of devices cannot be incorporated into the problem to be solved.

Correct objective technical problem?

- **Opponent**: avoiding the formation of deposits and clogging of devices using a liraglutide-containing formulations comprising an isotonic agent.
- **Patentee**: provision of liraglutide-containing formulations having improved manufacturability and usability whilst maintaining stability.

Decision on inventive step

- **Patent examples**: Simulated daily injections of the tested composition with the same needle and a simulated filling test that lasted for 24 hours
- **D3** primarily directed to improving the stability of GLP-1 peptide compositions
- **D3** does not require or suggest that the same needle should be used & does not describe anything like a 24 hour filling procedure
- Undesired phenomenon of compositions comprising mannitol would not inevitably manifest themselves upon practical implementation of D3

“The recognition of the relevance of these phenomena **should therefore be considered to form part of the technical contribution described in the patent**. A specific reference in the formulation of the objective technical problem to the avoidance of these phenomena risks to unfairly direct development towards the claimed solution, which is not permissible, as it introduces aspects of hindsight in the assessment of obviousness of the solution.”

Decision on inventive step

- Without the benefit of hindsight – knowledge of liquid state and lower viscosity of propylene glycol provided the skilled person with no suggestion that replacement of mannitol by propylene glycol would allow for optimization of the manufacture and usability of formulations of D3

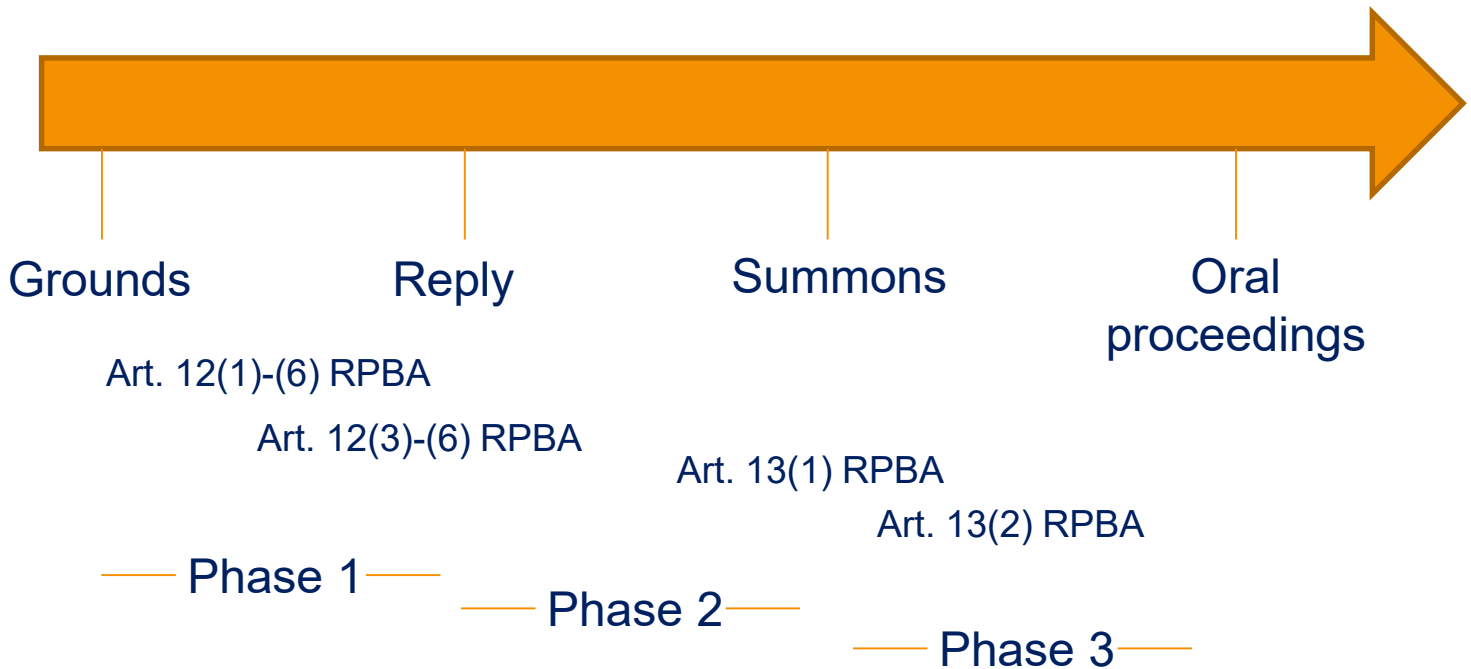
Discussion points

- Inevitable consequence of implementing the prior art vs discovery of an unrecognised problem
- Potential strategy for establishing inventive step
- Recognition that the solution itself may be obvious?

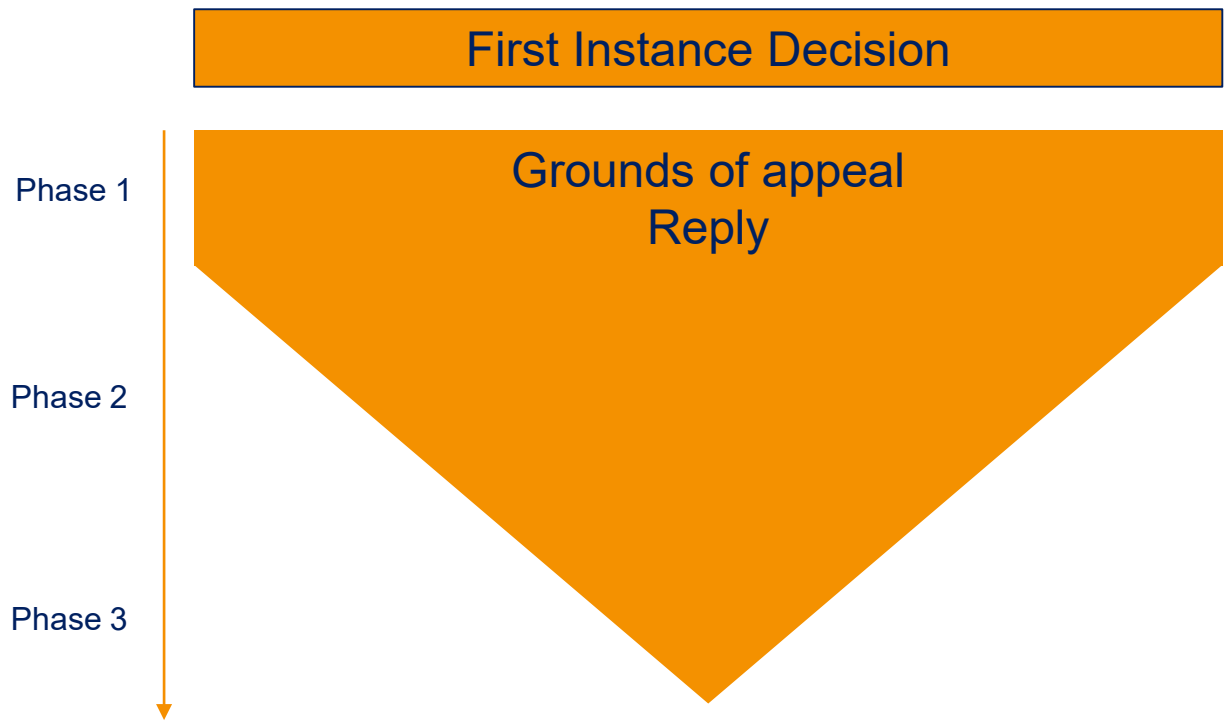
Update on Rules of Procedure of the Boards of Appeal - 2020

- Admissibility

Timeline of appeal



Judicial review + convergent approach



T 0892/21 – late filed documents – inventive step

Preliminary Opinion of Opposition Division:

- Included a statement that the data in the patent does not support a technical effect

First Instance Decision:

- Granted claims lack novelty
- Auxiliary requests lack an inventive step

Appeal Statement:

- Further auxiliary requests filed
- D22 – experimental data – filed to support the technical effect

T 0892/21 - appeal proceedings

Patentee arguments:

- D22 should be admitted
- D22 filed to “address a reason given in view of Article 56 EPC in page 10 of the appealed decision, namely the lack of evidence proving a technical effect of the superior amounts of components (b) and (c)”
- D22 is prima facie relevant

T 0892/21 – late filed documents – inventive step

Opponent reply:

- Disputed the admittance of D22
- Data not relevant
- Should have been filed earlier in view of preliminary opinion of Opposition Division
- Maintained that claims of all requests lack novelty/inventive step

T 0892/21 – Appeal Proceedings

Article 12 (2) RPBA

Basis of appeal proceedings

(2) In view of the **primary object** of the appeal proceedings to review the decision under appeal in **a judicial manner**,

a party's appeal case **shall be directed to the requests, facts, objections, arguments and evidence on which the decision under appeal was based**.

T 0892/21 – Appeal Proceedings

Article 12 (6) RPBA

Basis of appeal proceedings

(6) The Board shall **not admit** requests, facts, objections or evidence which were **not admitted** in the proceedings leading to the decision under appeal, **unless** the decision not to admit them suffered from an error in the use of discretion or unless the circumstances of the appeal case justify their admittance.

The Board shall not admit requests, facts, objections or evidence which should have been submitted, or which were no longer maintained, in the proceedings leading to the decision under appeal, unless the circumstances of the appeal case justify their admittance.

T 0892/21 – Board's commentary

- Opposition Division's preliminary opinion pointed to the absence of experimental data supporting the alleged technical effect
- "*The board finds that well before the oral proceedings that concluded the opposition, the appellants were already aware of the possible relevance of the lack of any evidence apt at proving the technical effect*"
- The filing of D22 **could and should have occurred during the opposition proceedings.**

T 0755/16 – documents & facts

- A018 – submitted by opponent with grounds of appeal
  - Two experiments
- A018 discussed in patentee reply to grounds of appeal – no objection to admittance
- During oral proceedings – patentee requested A018 not admitted

T 0755/16 – amendment to case?

- Request not to admit A018 raised for the first time
- During oral proceedings, patentee asserted that Experiment 1 of A018 was **not** in accordance with claim 1
  - Immunoglobulin concentration lower
- Patentee asserted this point was made in its reply to grounds of appeal

T 0755/16 – Board's commentary

- Patentee's reply to the grounds of appeal reads:

  "The parameters used in Exp 1 and Exp 2 do not match the values in the granted patent"

- The only parameter discussed in that context was the **cross-flow**
- **No** explicit or implicit reference to the difference between the **immunoglobulin concentration** of experiment 1 and that required in step iii) of claim 1.

T 0755/16 – Board's commentary

- Held: this request is an amendment to Patentee's case
- Article 13(2) RPBA:
  - any amendment after notification of summons to oral proceedings shall **not** be taken into account **unless** there are **exceptional circumstances** which have been **justified with cogent reasons** by the party concerned.
- Admittance could have been objected to before oral proceedings
- No reason why not done – no exceptional circumstances

T 0554/20 – late filed documents

- First instance : claim 1 of AR1 novel and inventive, and patent maintained as amended on basis of AR1
- Opponent appealed the decision

T 0554/20

- Preliminary opinion deviated from first instance decision: document O2 anticipates claim 1 of AR1
- In response, patentee submitted document O10 – this was filed to corroborate their novelty arguments on O2
- Filing of O10 constituted an amendment to the patentee's appeal case within the meaning of Article 13(2) RPBA 2020

T 0554/20

Article 13 (2) RPBA
Amendment to a party's appeal case

(2) Any amendment to a party's appeal case made **after the expiry of a period specified by the Board in a communication under Rule 100, paragraph 2, EPC** or, where such a communication is not issued, **after notification of a summons to oral proceedings** shall, in principle, **not be taken into account unless**

there are exceptional circumstances, which have been justified with cogent reasons by the party concerned.

Board’s commentary

- Patentee filed document O10 as a reaction to the board's preliminary opinion that claim 1 of AR1 was not novel over document O2, arguing the board had unexpectedly deviated from the opposition division's decision, which considered claim 1 allowable
- Opponent had already submitted detailed novelty arguments against claim 1 of AR1 based on document O2 in its grounds of appeal
- Patentee could and should have filed O10 already together with the reply to the grounds of appeal

Board’s commentary

- The mere fact that the board, in its communication pursuant to Article 15(1) RPBA 2020, came to a conclusion different from that of the opposition division **cannot be considered per se an exceptional circumstance** within the meaning of Article 13(2) RPBA 2020
- The board did not introduce any new objection either, but rather considered the objection of lack of novelty over document O2, which was already in the proceedings, persuasive in its communication.

Summary points

- Grounds of appeal and the appeal reply must contain your complete appeal case.
- Directed to the requests, facts, objections, arguments and evidence on which the Decision under appeal was based.
- If filed for the first time with grounds of appeal or reply – must explain why not filed during first instance.
- Very difficult to get any ‘amendments’ to your case admitted after Grounds of Appeal or the Appeal Reply.

Slides and a recording of this webinar will be emailed to you later this week.

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